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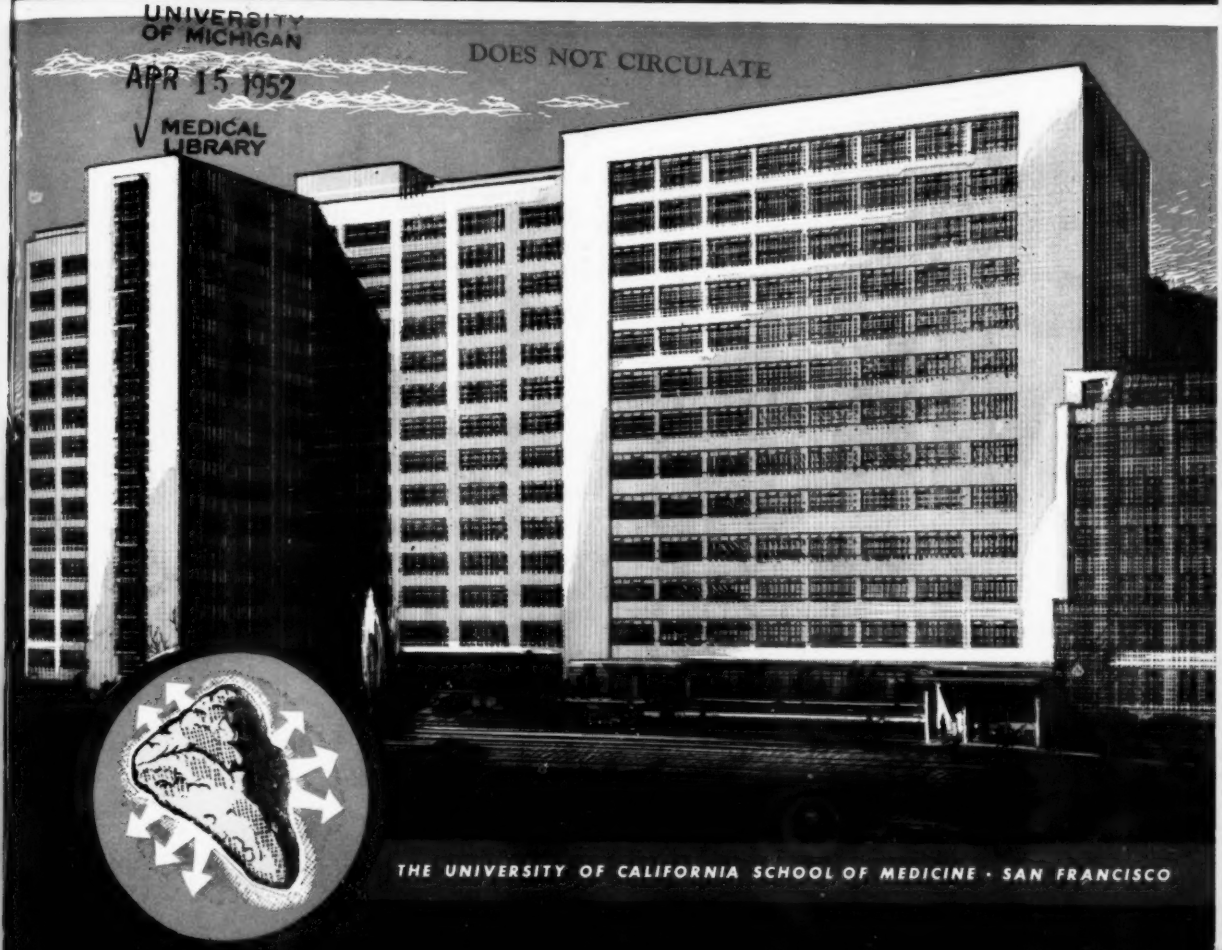

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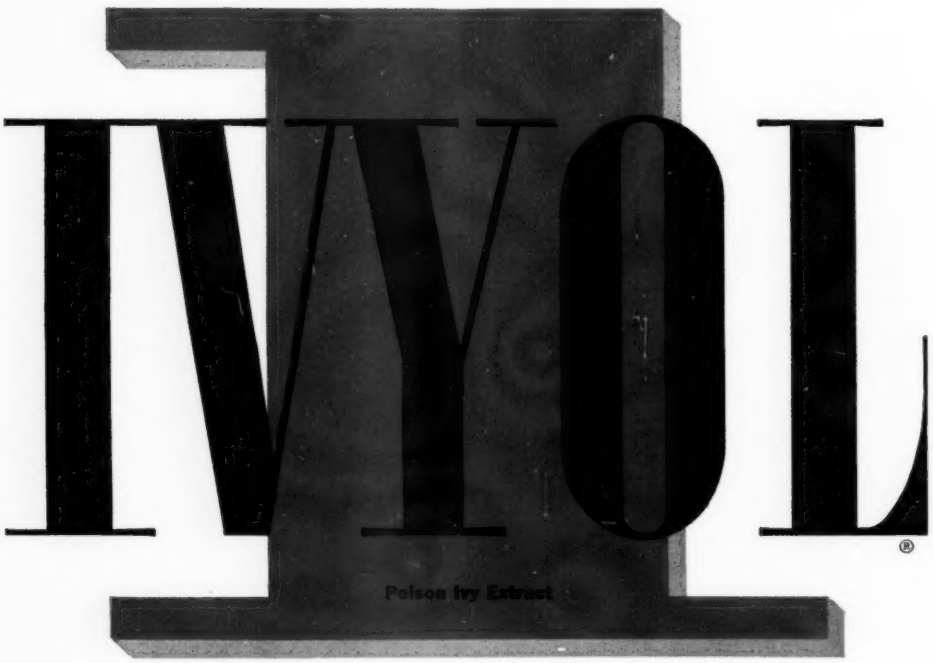
prelude to SUMMER MISERY



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FOREWORD

MEDICINE advances when the observational method and the research philosophy pervade both preclinical and clinical aspects. The interplay between careful observations from the clinic and careful analysis from the laboratory is essential for a well balanced school of medicine.

The frontier of medicine lies largely in the clinical fields, where initial terminologies and differentials must first point the way for further analysis and synthesis by laboratory technics.

For his pioneer role in the field of clinical endocrinology, Dr. Hans Lisser deserves singular recognition. As a former student of Dr. Lisser, I can speak both personally and for his school with admiration and affection. So many of his careful studies of patients have paved the way for subsequent appraisal by biochemical technics. The University of California School of Medicine in San Francisco is justly proud of these contributions from the students and associates of Dr. Hans Lisser which make up this issue.

Francis Scott Smyth

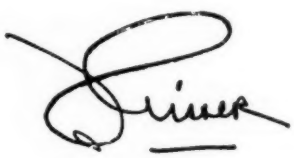
DEAN, UNIVERSITY OF CALIFORNIA
SCHOOL OF MEDICINE

ADRENAL HYPERFUNCTION

The history of changing and additional understandings in medicine provides numerous periods or epochs during which fertile studies in a certain branch or discipline greatly enriched medical knowledge and interpretation. The era of postmortem pathology, followed by that of bacteriology, and later by the epoch of the physiologic or functional approach constitute outstanding examples. Of late, astounding revelations have been contributed by the organic chemist, and right now this is brilliantly illustrated in the field of adrenal steroids.

Hence, it has seemed appropriate to present from the clinical side a series of syndromes of considerable variation, having, however, a common origin from tumorous growth or hyperplasia of the adrenals. In most of these, whether occurring in a boy or girl, a man or woman, the cytologic picture was found to be the same, but these same cells must have been elaborating steroids of quite different patterns.

It is to be hoped that more precise knowledge of the actual steroids responsible, recognition of the clinical manifestations produced, and better tests for verification of the specific steroids involved will result in better survival following surgical intervention.



GUEST EDITOR

FOLLOW-UP REPORT OF A 5 YEAR OLD SEXUALLY PRECOCIOUS BOY

20 Years After Removal of A Malignant Adrenal Cortical Tumor

H. LISSER AND LIONEL PLAYER

UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE, SAN FRANCISCO

IN 1933, the authors[1,2] reported a remarkable instance of sexual precocity in a boy who was 4 years and 11 months old when first seen by one of us (H. L.) in September 1931. He had a mustache, a fairly deep voice, the bone age of a 12 year old, the sexual hair of a 15 year old, and the external genitalia of a fully developed adult male (Figure 1a). As was to be expected in a case of this kind, he was tall for his age, 47⅛ inches, the upper limit of the most liberal estimate of height-range-for-age. He weighed 59 pounds, which was about 10 pounds heavier than is considered normal for a boy of his height and age, but this excess of weight was in the nature of muscular development; it did not consist of fat. His physical appearance, without consideration of his astounding sexual precocity, was nearer that of a boy 8 years of age than that of a lad barely 5 years old. He seemed quite normal mentally, neither dull nor brilliant. Fortunately, he was well behaved and had not made any embarrassing advances to girls or women, as has been reported in some cases of this kind—and this despite erections, almost nightly nocturnal emissions, a prostate of adult size, and a thick penis which was 3½ inches long when relaxed. The prostatic secretion contained a considerable amount of lecithin and numerous spermatozoids.

From the Divisions of Medicine and Surgery (Urology), University of California School of Medicine, San Francisco, California.

LISSER

PLAYER

No tumor could be palpated, but retrograde pyelography revealed a mass above the left kidney. The kidney was displaced downward, the pelvis bent down and outward at a sharp right angle, and the upper calyx was depressed and somewhat flattened (Figure 2a).

On December 7, 1931, one of us (L. P. P.) removed a well encapsulated adrenal tumor, slightly larger than a good-sized apple. It measured 7.5 by 9 cm. and weighed 278 gm. Microscopically, it was composed of adrenal cortical cells, varying greatly in size and shape, with some multinucleated cells which appeared to be rapidly growing, relatively undifferentiated, and probably malignant. The boy's recovery from the operation was quite satisfactory without supportive therapy with adrenal extract, and he was discharged from the hospital 18 days later.

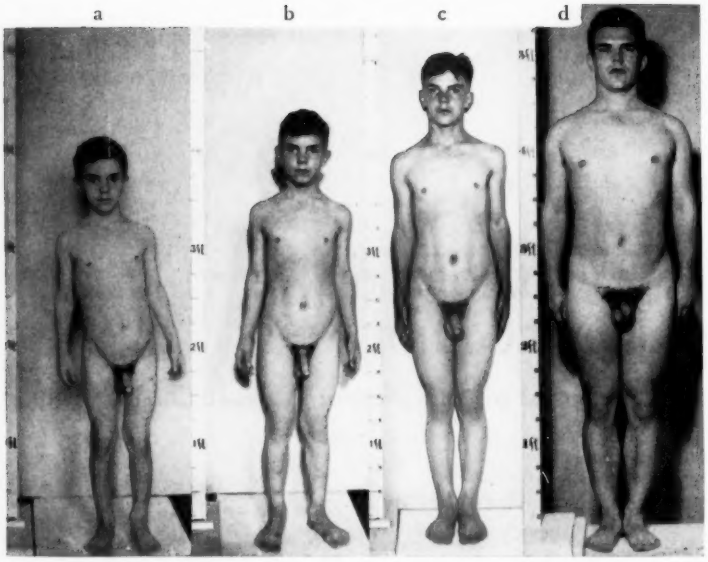


FIGURE 1a. Patient, age 5 1/12 years. Before operation. Note tallness for age, mustache, pubic hair and adult-sized genitalia. b. Same patient, age 6 4/12 years. One year and two months after removal of adrenal tumor. Grown 5 inches. c. Same patient, age 8 11/12 years. Grown 8 inches in past two and a half years. Note muscular build and massive thighs. d. Same patient, age 21 4/12 years. Grown 4 3/4 inches since previous photo, but only 1 inch after 13 1/2 years of age. Note husky physique.

During the subsequent 18 months, he was observed regularly once a month. No spectacular changes occurred with regard to his sexual status; that is, there was no diminution in the size of the external genitalia or dropping out of the precocious growth of axillary, pubic or facial hair. Erection and nocturnal emissions, however, occurred far less frequently. Also, his demeanor was more childish, happier and quieter, less strained and tense, less bashful and self-conscious. The rate of skeletal growth continued to be excessive, almost 5 inches during the year 1932, the normal rate of growth being slightly over 2 inches during this age period. At just 6 years of age, his height was 52¼ inches, at least 2½ inches above the extreme upper limit of height-range-for-age; the average height for a boy of this age is 44 inches (Figure 1b).

Intravenous urograms, 15 months after operation, showed the left kidney back in normal position, with excellent filling of the left renal pelvis and calices. The blood pressure had decreased to 92/40, as compared to 114/70 when the patient was first seen and to 134/80 a few months later. At 6 years of age, his dental age was considered equal to that of a 10 year old child, four upper and four lower permanent incisors having erupted. Spermatozoids were no longer to be found in his prostatic and seminal vesicle secretions.

In November 1934, when he was 8 years and 1 month old, the boy's height was 58¾ inches; he had grown 11½ inches in three years and two months, whereas average growth for that age period would be nearer 6 inches. At this time, the bone age was estimated at 15 years, 7 years' acceleration. During the following 10 months, this rapid rate of growth subsided, so that in September 1935, his height had reached only 60⅜ inches (Figure 1c). In the succeeding two and one-half years he grew but 3½ inches, and only ½ inch during the next two years. Accordingly, when he was 13½ years old, his height was 64¼ inches.

He was not seen again until November 1947, when he was 21 years old (Figure 1d). At that time, his height was 65⅛ inches. He had a husky, stocky build, with massive thighs and relatively short legs. It is interesting to contrast the swift and abnormal growth of 11½ inches between 5 and 8 years of age with the meager increment of 5½ inches between 8 and 13½ years of age, and only 1 inch afterward, eloquent evidence of premature closure of the epiphyses.

By the time he was 8 years old, the boy's thighs were conspicuously muscular, but although he was strong, he was not Herculean, and no exceptional feats of strength had been noticed. He was not pugnacious nor unduly

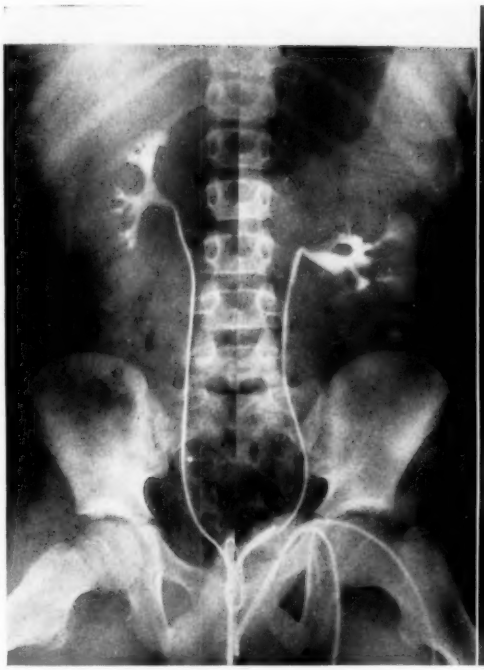


FIGURE 2a. Pyelogram, 1931. Note flattening and dislocation downward of upper calyx, left kidney.

FIGURE 2b. Pyelogram, 1948. Left kidney calices in normal position.

interested in or attracted to the opposite sex; erections and nocturnal emissions had ceased. When the lad was 9 years old, his father remarked that he had the interest in and aptitude for mechanical work of a young man of 16 years and enjoyed helping with the servicing and repair of an automobile. When he was 10 years old, he played football, liked shop work and was obtaining satisfactory grades in school.

In April 1948, this young man, at 21½ years of age, was a normal, healthy student at a nearby university. A few months before, although a recurrence either in the form of cortical hyperplasia or malignancy was most unlikely 17 years after surgical removal of an adrenal tumor, a 24 hour specimen of urine was assayed and the total excretion of 17-ketosteroids was reported as 15.5 mg., well within the normal range for an adult male. It is gratifying that successful extirpation of the well encapsulated adrenal tumor was performed in time to permit growth of the patient to normal height, and, more important still, in time to save his life before metastases had occurred.

Sexual precocity in boys falls into three categories: (1) familial sexual precocity in consecutive generations, without any pathologic lesion;[3] (2) postencephalitic, following measles, mumps or whooping cough, presumably complicated by encephalitis in the region of the fourth ventricle; (3) endocrine, due to tumor or hyperplasia of the adrenal cortex, or tumor of a testicle or of the pineal gland.

The first two categories could be ruled out at once in this case, as could testicular tumor. Absence of signs of increased intracranial pressure and of signs of pressure on the corpora quadrigemina eliminated a pineal tumor. Consequently, an adrenal tumor was suspected, was established on the left side by pyelography, verified at operation, and confirmed pathologically. Twenty years later, the patient is perfectly well. Prior to 1931, there had been only three similar cases of boys with sexual precocity due to an adrenal tumor in which surgery was attempted. Two proved inoperable, and the third boy died 24 hours after operation.

In adenoma, carcinoma and hyperplasia of

the adrenals, excessive amounts of adrenal cortical steroids are usually produced. An understanding of the biologic properties and the clinical and metabolic changes they produce in the body is essential to the institution of proper therapy. The adrenogenital syndromes, to quote Cahill,[4] "are determined by the type and amount of hormones produced and by the sex and age of the patient." Certain steroids of adrenal origin are known to exert specific influences on: (1) fluid and electrolyte balance, (2) protein deposition (anabolic), or (3) sugar and fat metabolism. Typical of the first category is the synthetic steroid, desoxycorticosterone acetate. It causes retention of water and sodium chloride and the elimination of potassium because of its action on renal tubules. This activity has made it invaluable in Addison's disease. Any excessive amount can cause hypertension and lead to cardiac failure. Steroids of the second category possess androgenic properties and are therapeutically and structurally similar to testosterone or resemble estrogens and have feminizing properties.[5] Excess of compounds of the third type results in the metabolic aberrations typical of Cushing's syndrome.

If, in a given case, a boy shows evidence of sexual precocity only, then a determination of 17-ketosteroid excretion[6] in a 24 hour total urine sample is desirable, provided there is a laboratory equipped to perform this assay. In localities without such laboratory facilities, 10 cc. of concentrated hydrochloric acid can be added to the urine and the total 24 hour specimen sent on for study. The normal range in adult males is 8 to 22 mg. per 24 hours, but before puberty the range in boys under 8 years of age is 0 to 2 mg.

If, in addition to signs of sexual precocity, the boy has symptoms or signs suggesting deficient production of the other adrenal cortical steroids (nonandrogenic), with a clinical picture resembling Addison's disease or an impending crisis of adrenal failure, then additional tests should be made to determine the levels of blood sugar, sodium, potassium, chlorides, and nonprotein nitrogen. In other words, adrenal cortical hyperplasia may result in excessive production of androgens, together with deficiency of the salt-retaining corticosteroids.[7-9] Operation to arrest the precocity in such cases is not recommended, since it would involve subtotal bilateral adrenalectomy. Such a procedure is hazardous and necessitates substitution therapy for life.

There are those who insist that both adrenals should be exposed before a tumor is removed from one of them. With this we do not agree. Such exposure merely informs one of the presence and size or of the absence of the other adrenal. Its appearance gives one no clue to its functional integrity, and there is no practicable method at present for appraising the function of each adrenal separately, as in the case of the kidneys. Bilateral exploration increases rather than minimizes the surgical risk.

If an adrenal tumor is strictly virilizing, whether it occurs in a boy, girl or woman, the opposite adrenal is less apt to be seriously impaired with respect to its normal functions. Accordingly, there is less need for apprehension in removal of the tumor, provided prophylactic supportive treatment is administered before, during and after operation to tide the patient over any temporary adrenal depression. However, if the adrenal tumor is associated with a clinical picture of Cushing's disease, namely, with derangement of electrolyte and carbohydrate metabolism, then atrophy and severe functional insufficiency of the opposite adrenal is to be anticipated[10] and operation should be undertaken only with full realization of the additional risks involved.

After an adrenal tumor has been suspected on grounds of the clinical endocrine disturbance, the next step, obviously, is to determine which adrenal is responsible. As a rule, these tumors are not large enough to be palpated, since they are up under the diaphragm and above the kidney. Retrograde pyelography or intravenous urograms,* as a rule, will localize the tumor by showing the downward and outward dislocation of the kidney and the flattening of the upper calyces (Figure 2a). There may be instances in which the tumor is not large enough to produce such distortion. In such cases, perirenal air or gas insufflation, followed by x-ray films, is advocated by Carelli,[11] Cahill,[12] Barquin[13] and others, but insufflation is not without danger, since air embolism may result despite careful precautions.

Our review of the literature to date discloses only one other case (that reported in 1942 by

*Intravenous urograms, if convincingly positive, are more convenient than retrograde pyelograms, but a negative report should not be accepted with complete reliance. One of us (H. L.) is conversant with an instance in which a fairly large adrenal tumor, which had been missed by the roentgenologist reading the urogram, was found after insufflation of air in the perirenal area.

Reilly[7]) of survival of a boy after removal of an androgenic adrenal tumor. In this case, the boy's sexual precocity was evident when he was 2 years old. At the age of 5½ years, he had an episode of pain in the right upper portion of the abdomen and hematuria, both of which subsided. One year later, he had a recurrence of the same symptoms, plus fever, abdominal distention, pain and rigidity. A mass appeared in the right upper quadrant, and within 12 hours the boy was delirious and stuporous. Although repeated laboratory tests were at variance and did not fully substantiate his diagnosis, the clinician applied supportive and therapeutic measures to combat suspected addisonian crisis caused by hemorrhage due to degenerative changes in an adrenal cortical tumor.

The treatment was symptomatic and consisted of administration of whole adrenal extract, desoxycorticosterone acetate, glucose and salt solutions, blood transfusions, opiates and cardiac stimulants. After 10 stormy days, the patient's condition finally allowed modification of treatment. Intravenous pyelograms at this time revealed a tumor in the region of the upper pole of the right kidney. Thirty-two days after the initial onset of the symptoms, the adrenal tumor was removed by the late Dr. Clark Johnson of San Francisco. The operation was difficult. Two hours after operation, the blood pressure rose, then suddenly fell and continued to fall. Treatment for adrenal deficiency was resumed; in 27 hours the patient received 30 mg. of desoxycorticosterone, 64 cc. of whole aqueous adrenal extract (ESCHATIN®) in divided doses and 4500 cc. of fluid (blood, glucose and saline solutions), along with opiates and cardiac stimulants, which successfully tided him over the crisis. Five months later, an excessive amount of 17-ketosteroids (5.6 mg. in 24 hours) was found in the boy's urine.

The principal reason for narrating some of the highlights in Reilly's case is that his is the *only other example, besides our own, of a sexually precocious boy who survived removal of an adrenal tumor.* The boy is still alive and well. Also, we desire to salute a very keen diagnosis and to call attention to the efficacy of the therapeutic agents he employed so skillfully in staving off an almost certainly fatal outcome from critical adrenal deficiency.

One of the more recent and eminently scientific contributions is that of Goldstein and associates,[14] under the title "Carcinoma of the adrenal cortex with the adrenogenital syndrome in children." These authors reported an extraordinary case, in which a preoperative diagnosis was made by means of tumor material obtained by punch biopsy. Three days later a successful operation was performed upon the patient, a girl 8 months old, the youngest child ever reported as having survived removal of an adrenal tumor. In an exhaustive review of the medical literature up to 1946, Goldstein and his associates listed a total of 54 reported cases in children. Analysis revealed 6 cases in which male children had been operated upon for an adrenal cortical carcinoma which had caused sexual precocity. In 2 of these 6 patients, the tumor was inoperable, 2 of the children died during operation, one died postoperatively from hemorrhage, and one from shock. In other words, none survived. Twenty-five female children were operated upon, 9 successfully; one of these, a 2 year old girl, was reported by Reilly, Lisser and Hinman.[15] The remaining 23 cases reviewed were those of autopsied subjects, 6 of whom were male children; none had been treated surgically.

A later compilation by Wilkins[5] tabulated 70 cases of adrenal tumors in children 12 years or younger.* Of 53 girls, 32 were operated upon and 11 cured; operation was attempted in 9 boys, 3 of whom were cured. The tendency of adrenal tumors to malignancy is shown by the fact that metastases occurred in 30 of the 70 patients.

*Wilkins[5] also reported the successful removal of a *feminizing* adrenal cortical tumor causing gynecomastia in a 5 year old boy, the only instance of this kind so far published. The boy was reported alive and well four years after operation.

References cited in this article will be included in the authors' reprints.

SUCCESSFUL SURGICAL REMOVAL OF ADRENAL CORTICAL ADENOMA CAUSING VIRILISM FOR 30 YEARS

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THE complexity of adrenal cortical function is indicated in part by the number of different clinical pictures which can be produced by a tumor of the cortical tissue. These clinical syndromes include: (1) precocious puberty in boys (Lisser[1]), (2) gynecomastia in boys (as reported recently by Wilkins[2]), (3) pseudosexual precocity of masculine direction in girls (Reilly, Lisser and Hinman[3]), (4) virilization in girls and adult women, (5) gynecomastia in adult men (Lisser[4]), and (6) Cushing's syndrome in either sex.

The tumors causing these dissimilar clinical pictures cannot be differentiated pathologically and appear essentially identical on microscopic study. Many of them have the characteristics of malignancy and, if not well encapsulated, may metastasize and progress to a fatal outcome. Others are classified pathologically as malignant, even though the symptoms they cause have been present for as long as 10 to 15 years. Still other tumors are found which have existed without causing any apparent endocrine manifestations in the patients. In all likelihood the future will disclose chemical reasons for these wide variations in symptomatology.

A high level of 17-ketosteroid excretion has been a frequent, though not invariable, finding in patients with adrenal cortical adenomas or carcinomas. The average normal excretion is now considered to be 5 to 15 mg. per 24 hours in adult men. In patients with adrenal cortical tumors, values from 50 mg. to over 1000 mg. have been reported.[5] It is possible to separate the 17-ketosteroids into alpha and beta fractions with digitonin. Normally, the beta fraction is low, and earlier reports indicated that any elevation above 5 per cent was suggestive of adrenal cortical carcinoma. Later, more extensive experience has indicated that this is not always true. In one medical center it is now the rule to assume that if the 17-ketosteroid excretion is over 50 mg. and the beta fraction is over 50 per cent, the patient probably has an adrenal cortical carcinoma.[6] Nearly all patients with excretion in the higher levels (over 200 mg.) reported to date have had adrenal cortical tumors which, when examined, were considered carcinomas. It must be reemphasized, however, that lesser elevations and even normal levels do not exclude the finding of a malignant cortical tumor.

ESCAMILLA

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SURGICAL APPROACH

The surgical approach depends on whether it has been possible to determine the location of the tumor before operation. It must be remembered that pyelograms, either intravenous or retrograde, do not always indicate the side involved, and also that adrenal tissue may be found in other locations in the abdominal cavity (especially near the ovaries). Perirenal air insufflation, which permits the visualization of an

adrenal tumor not revealed by other x-ray maneuvers, could be helpful in such instances. Since this procedure has caused fatalities in our clinic, it was avoided in this case. It is possible that the recent use of carbon monoxide gas instead of air may make perirenal gas insufflation a safer method.

When the location of the tumor cannot be determined, the ideal surgical approach is by means of an upper transverse abdominal incision. Through this incision, both adrenals can be inspected, the pelvis examined, and the tumor, whatever its site, removed. If the location of the tumor has been established positively before operation, the combined thoraco-retroperitoneal approach, as advocated by Chute and Soutter,[7] is preferable. If the tumor is small, or if the patient is a poor surgical risk, a lumbar retroperitoneal approach is indicated. In the latter case, if a better exposure can be gained by dividing the diaphragm, it is best to use an endotracheal anesthesia.

SPECIAL PREPARATION AND CARE BEFORE, DURING AND AFTER OPERATION

The preparation for surgery and the care of the patient during and after operation are extremely important factors in achieving a successful outcome. Present day plans usually include the use of cortisone with desoxycorticosterone and salt. One such plan has been reported by Huggins and Bergenstal[8] to be satisfactory in bilateral adrenalectomy. In our patient, the liberal use of adrenal cortical extract and glucose with salt proved safe. The details concerning quantities and administration are given later in this discussion.

In the course of the operation, the patient's blood pressure must be watched carefully, especially during manipulation of the tumor and after its removal; however, blood pressure fluctuations are not as spectacular or as dangerous as those which occur during the removal of a pheochromocytoma composed of medullary chromaffin tissue. Adrenal cortical extract should be ready for immediate intravenous injection if needed. The usual supplementary methods of combating shock should be employed if they are required.

After the operation, the patient should have a special nurse, and a house physician should be in almost constant attendance. The blood pressure should be checked every 5 to 15 minutes during the first 24 hours, and almost as often during the next three or four days. Injections of adrenal cortical extract probably will be necessary during this period; the amount to be given will depend upon the level of the patient's blood pressure. In case of critical emergency, a supply of the aqueous extract (50 to 100 cc.) should be kept ready for immediate injection.

The patient in this report withstood surgery successfully. Her tumor showed some malignant characteristics, even though symptoms of virilization had been present for 30 years. It was well encapsulated. At this time (31 months after removal of the tumor), no evidences of recurrence are discernible.

The case report which follows gives the details of surgical management. It also illustrates the rapidity with which an abnormally high 17-ketosteroid excretion drops to normal levels after removal of a tumor of this kind.

CASE REPORT

Mrs. L. P., 63 years old, was seen in consultation at St. Mary's Hospital, San Francisco, at the request of Dr. R. E. De Weese. She had been in normal health until the age of 33 years, when she developed permanent amenorrhea, following her third pregnancy, and noted gradually increasing hirsutism. The hair growth had appeared over her entire body, and the beard growth finally became so vigorous and heavy that for the last several years she had been forced to shave daily. The scalp hair had gradually thinned and fallen out, resulting in typical male baldness. Hypertension had been known to be present for several years but had not produced any serious complications. Symptoms of vertigo and headache, however, first caused her to seek medical advice.

Examination showed a tall, rather thin woman with an erect posture (Figure 1). The heavy beard growth, hirsutism and baldness were most striking (Figure 2). Her voice was slightly husky but of feminine quality. Her blood pressure was 200/100, but later averaged 165/90. The clitoris was approximately three times the normal size (Figure 3).

X-ray films of the skull and chest showed no abnormalities. Intravenous pyelograms failed to reveal definite evidence of adrenal tumor. Cholecystograms showed normal function and a

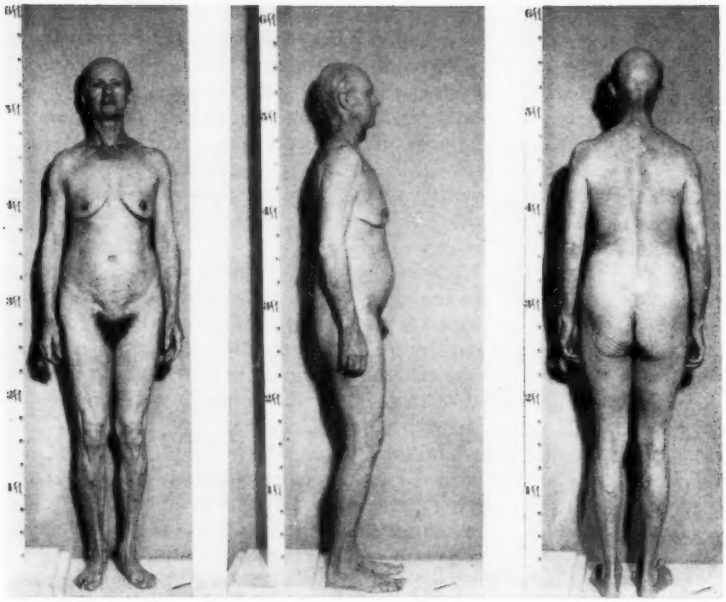

FIGURE 1a, b and c. Appearance of patient before operation.

somewhat enlarged liver. Results of a glucose tolerance test were as follows: fasting, 95 mg. per cent; one-half hour, 200 mg. per cent; two hours, 285 mg. per cent; three hours, 219 mg. per cent. The basal metabolic rate was plus 19 per cent. The 17-ketosteroid excretion in the urine was 456 mg. (total neutral) per 24 hours Further 17-ketosteroid studies in the laboratory of Dr. Gerson Biskind showed the total neutral 17-ketosteroids to be 661 mg.; another 24 hour specimen was assayed at a ketonic level of 663 mg. Fractionation revealed the alpha fraction to be 571 mg. and the beta fraction 170 mg. (23 per cent), the total of these two being 741 mg. for that 24 hour period.

The amenorrhea, hirsutism, enlarged clitoris and very high 17-ketosteroid excretion made the preoperative diagnosis of adrenal cortical tumor almost a certainty, although the site was not localized by roentgenography. Previous unfortunate fatalities from perirenal air insufflation caused us to decide against this as a method of further investigation.

At this time, the course was interrupted by a urinary infection which caused some fever, but which responded to treatment with streptomycin. The patient was considered ready for operation on December 8, 1948.

Preoperative medication consisted of 5 cc. of lipoadrenal cortical extract injected intramuscularly at 8 P.M. the night before and 5 cc. at 7 A.M. the day of surgery. One thousand cubic centimeters of 10 per cent glucose in Ringer's solution was administered in the morning before operation, and another 1000 cc. was running at the time the operation was started.

OPERATION

THE patient was operated upon by S. G. J. under endotracheal gas and oxygen anesthesia, with intravenous administration of curare. First, a lower midline incision was made, through which the pelvis was explored. The uterus and tubes appeared normal; the ovaries were atrophic. Manual exploration of the right upper quadrant revealed a mass the size of a large grapefruit just above the right kidney. No mass was felt on the left. The incision was then lengthened superiorly to the left of the umbilicus. A rent was made in the gastrohepatic ligament and the left adrenal was exposed. It was normal in appearance but quite small.

The abdominal wound was closed and dressed, after which the patient was turned onto her left side. A posterolateral lumbar extraperitoneal incision was made. The mass above the right kidney was then freed on its lateral and inferior

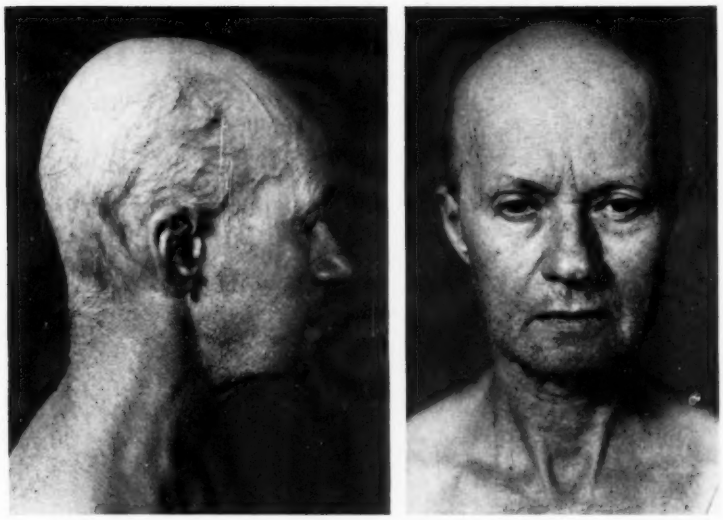

FIGURE 2a and b. Closeup of face before operation. Beard growth is of four days' duration. Note typical masculine baldness.

surfaces. It was considered hazardous to attempt to separate the mass on its superior and medial aspects without better exposure because of the numerous large blood vessels which entered from the medial and posterior sides. The incision was lengthened superiorly in the paravertebral region, the eleventh rib excised, and the tenth and ninth ribs divided. Through the right pleural space the right diaphragm was incised at the junction of its lateral and medial thirds. This combined thoraco-retroperitoneal approach provided adequate exposure.

It was seen that the tumor arose from the right adrenal (Figure 4) and was well encapsulated. Approximately 3 gm. of normal-appearing adrenal tissue was attached to its medial side. There were no enlarged retroperitoneal nodes. The right kidney, which appeared to be normal, had not been invaded. The tumor was freed and removed, a portion of the normal-appearing adrenal tissue being left in place.

After fragments of the divided ninth and tenth ribs were approximated with small stainless steel wire, the wound was closed with interrupted fine cotton sutures. The large dead space left after removal of the tumor was drained.

Medication during the operation consisted of 5 cc. of lipoadrenal extract at 10:40 A.M., when the blood pressure was 120/60. Five hundred cubic centimeters of blood was given at 10:50 A.M. and a unit of plasma at 12:35 P.M., when the blood pressure was 150/80.

During the first 24 hours after the operation, the blood pressure fluctuated between 140 and 210 systolic over 80 to 120 diastolic. During this period the patient received 15 cc. of lipoadrenal cortical extract, 1500 cc. of whole blood, and 2000 cc. of 5 per cent glucose in water. During the second 24 hours, 17 cc. of lipoadrenal cortical extract, 10 cc. of aqueous adrenal cortical extract, 500 cc. of whole blood, and 2000 cc. of 5 per cent glucose in water were administered. The blood pressure varied from 120 to 175/60 to 80. During the third 24 hours, the patient received 8 cc. of lipoadrenal cortical extract and 1000 cc. of glucose in Ringer's solution. The amount of adrenal cortical extract then was gradually decreased until the eighth postoperative day, when administration was stopped. On the thirteenth postoperative day the patient complained of some left anterior chest pain. She had a slight cough but no hemoptysis. These symptoms were thought due to a pulmonary embolus, probably from a phlebothrombosis in the left calf. Since adequate prothrombin readings could not be taken, ligation of the superficial femoral veins was performed by S. G. J. Otherwise, gradual recovery from the operation was without incident.

On December 15, 1948, only one week after the operation, the 17-ketosteroid excretion had dropped to 15.8 mg. per 24 hours (the preoperative level was 741 mg.). An x-ray film of the chest on that day showed some fluid in the

right pleural cavity; later serial x-ray studies demonstrated gradual improvement, although the right diaphragm remained high.

One month after the operation, the 17-ketosteroids were 9.1 mg. per 24 hours. After two months, the patient felt considerably stronger. She thought that the hair growth was less vigorous, although daily shaving was still necessary. Her blood pressure at this time was 160/80. A repeat 17-ketosteroid estimation was 10 mg. per 24 hours. Three months after the operation, the 17-ketosteroid excretion was 5.6 mg. per 24 hours (total neutral). The patient noted that her skin was somewhat softer, and she thought that the beard growth had abated somewhat, although it was still necessary to shave six days a week. She returned to work after a four month period.

Five months after the operation, the 17-ketosteroid excretion was 11.2 mg. per 24 hours. One month later the patient reported that although she still shaved every day, it was now necessary to shave the upper lip only every four days. There had been no regrowth of hair on the scalp. Her blood pressure was 150/90. A glucose tolerance curve taken at this time showed a striking improvement in carbohydrate tolerance. It was as follows: fasting, 140 mg. per cent; one-half hour, 196 mg. per cent; one hour, 140 mg. per cent; two hours, 104 mg. per cent; three hours, 82 mg. per cent. (The preoperative curve was: fasting, 95; one-half hour, 200; one hour, 258; 2 hours, 285; 3 hours, 219.)

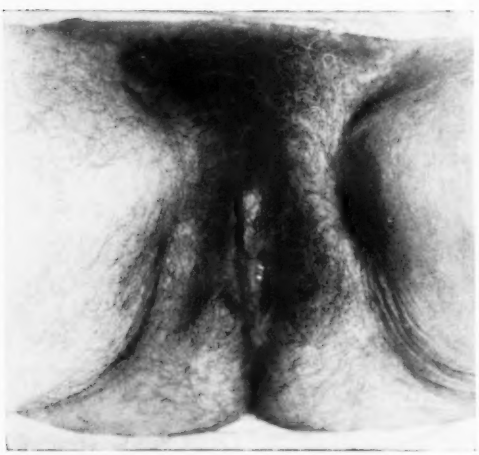

FIGURE 3. Closeup of external genitalia. Note protrusion of large clitoris from between labia.

FIGURE 4. Delivery of tumor from wound at time of surgery.

Nine months after removal of the tumor the 17-ketosteroid excretion was 16 mg. per 24 hours, and at 10 months, 13.1 mg. per 24 hours. The rate of hair growth remained the same.

At a recent follow-up visit, 38 months after operation, the patient was in satisfactory physical condition, with a blood pressure reading of 120/70. The hair growth was unchanged, only slightly less than before the operation. The 17-ketosteroid excretion was 7 mg. per 24 hours.

PATHOLOGIC REPORT

The pathologic report by Dr. A. M. Moody was as follows: "The tumor measured 17.5 by 12 by 8.5 cm. and weighed 1,058 gm. (Figure 5). It appeared well encapsulated. There were large tortuous vessels over its surface, and the mass itself felt cystic. On section it was found to be a solid tumor, relatively soft and containing areas of apparent degeneration and hemorrhage.

"Microscopic examination showed the tissue to resemble that of adrenal cortex (Figure 6), although the cells were irregular in size and shape and in grouping, and appeared to have some of the characteristics of malignancy. There were some areas of fatty tissue and irregular areas of degeneration and hemorrhage.

"Diagnosis: Malignant type of adrenal adenoma, well encapsulated. Virilism."

DISCUSSION

This case illustrates the fact that a large adrenal tumor can exist without indicating its

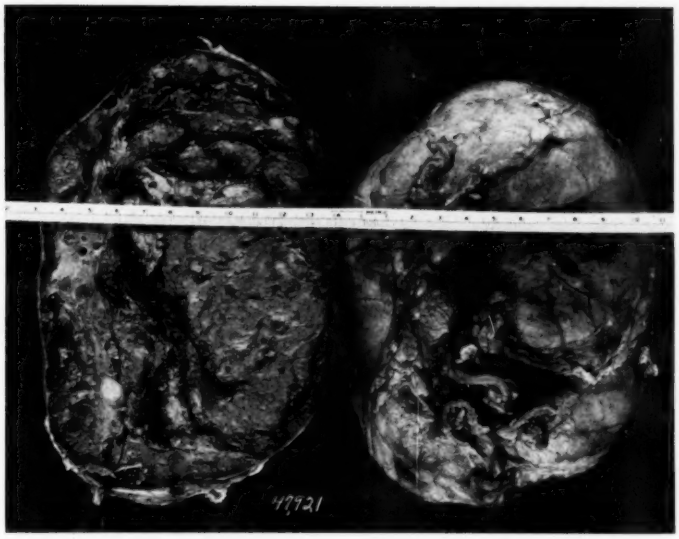

FIGURE 5. Gross appearance of capsule and cut section of tumor.

presence on an intravenous pyelogram. In such instances, there is a choice between taking the risk of a perirenal gas insufflation for further study or awaiting surgical exploration to determine the exact location of the tumor. In our experience, there is less risk from the surgical exploration.

In retrospect, it is possible that abdominal exploration and excision of this tumor might have been accomplished more easily and with less trauma to the patient through a transverse upper abdominal incision.

The importance of preoperative preparation and postoperative care, with the administration of adequate amounts of cortisone and desoxycorticosterone or of adrenal cortical extract, glucose, and salt, must be emphasized.

The microscopic appearance of the tumor is of some interest because of the characteristics of malignancy which were found, although symptoms had been present for 30 years. Evidently, these tumors, despite their malignant characteristics, can pursue a benign course for many years if they remain well encapsulated.

It is also of interest that the mild diabetes of the patient had practically disappeared six months after the adrenal tumor was removed. The disappointingly slight decrease in the rate of beard growth suggests that an abrupt and spectacular change may not be expected in a pattern which has persisted for over 30 years.

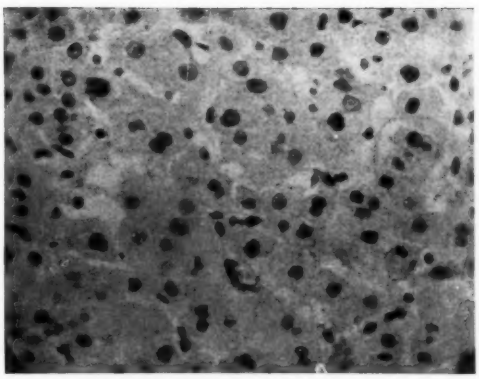

FIGURE 6. Microscopic appearance of tumor.

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ADRENAL CORTICAL CARCINOMA WITH EXCESS ANDROGEN PRODUCTION IN AN ADULT MAN

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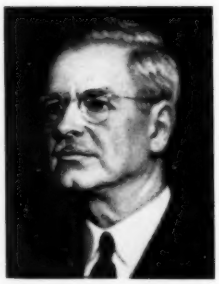
THE patient with an excess or deficiency of one or more hormones presents a diagnostic challenge to the clinician. The problem may be simple or difficult, depending upon how much is known of the specific actions in man of the hormones in question. The situation involves many factors, including patient's age at onset, sex, racial and familial characteristics, nutritional state, environmental factors too numerous to mention, and variations in individual responses.

When excessive androgenic steroidal hormones are liberated, manifold clinical syndromes may present themselves, depending primarily on the age and sex of the patient. If this overproduction begins *prenatally in female subjects* (congenital adrenal cortical hyperplasia), the clinical syndrome known as female pseudohermaphroditism is found.[1] The same hormonal anomaly originating postnatally in the *preadolescent girl* is perhaps best described as pseudosexual precocity.[2] In the *preadolescent boy,* a condition of precocious puberty accompanied by "infant Hercules" characteristics is the clinical manifestation of this same excess of adrenal or testicular androgens.[3-8] In the *adult female,* excess androgen production of adrenal or ovarian origin results in virilism.[9] Excessive androgen production in the *adult male* is exceedingly rare, having been reported in association with interstitial cell tumors of the testis in only four instances.[10-13]*



KERR

GORDAN

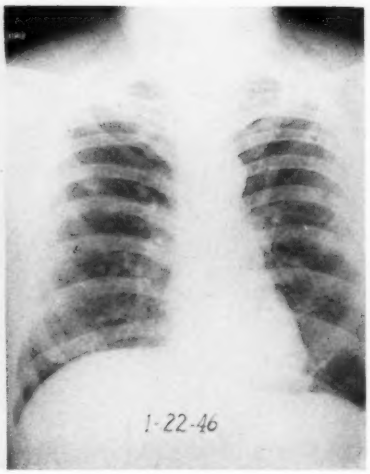
It is the purpose of this paper to report a similar syndrome in an adult male, with the distinction that the source of androgen in this patient was an adrenal cortical carcinoma, and to stress its anabolic consequences.

CASE REPORT

The patient, a 44 year old married man and father of two children, was referred to one of us (W. J. K.) by Dr. G. S. Delamere of Marysville, California. He entered the University of

From the Division of Medicine, University of California School of Medicine, San Francisco, California.

*Budd's case,[13] although described as an interstitial cell tumor, was associated with production of estrogen and may have been a Sertoli cell tumor.



FIGURES 1 and 2.

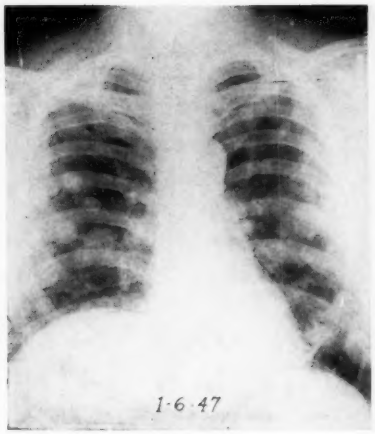
California Hospital in January 1942, because of an upper abdominal mass noticed two months previously. He had been in good health until six months earlier, when he had developed nausea, postprandial abdominal discomfort, and severe weight loss from an accustomed 205 pounds to 145 pounds. X-ray studies had demonstrated a duodenal ulcer, and the patient had been treated with diet and powders, with good results. His symptoms disappeared; he again felt well and was able to eat all types of food without discomfort. His weight stabilized at 168 pounds. After the abdominal mass was first noted in December 1941, a laparotomy done elsewhere disclosed a large, doughy, vascular tumor filling the entire right upper quadrant. A biopsy was reported to show carcinoma of uncertain origin, and the patient entered the University of California Hospital for roentgenotherapy.

Upon examination, a large, firm, nontender mass was found below the right costal margin. Both breasts were enlarged and tender, but no secretion could be expressed. There was no lymphadenopathy and a rectal examination disclosed a normal-sized prostate. Testes were of normal size and consistency; there were no abnormalities of voice, hair or pigmentation. Blood pressure was 135/85. The remainder of the examination disclosed nothing unusual, and revealed only alopecia capitis and an old right facial palsy.

Laboratory tests—Blood count: hemoglobin 12.2 gm.; RBC 4,360,000; WBC 10,000 per cubic millimeter with a normal differential count. Urine: normal. Stool: negative for occult blood. Icterus index 5.0. Rose bengal and intravenous galactose tolerance tests for liver function were normal. Phenolsulfonphthalein excretion test for renal function showed 77 per cent in two hours. X-ray films showed no abnormalities. Intravenous pyelograms (Figure 1) showed a large mass in the right upper quadrant displacing the kidney downward.

X-ray therapy was administered by Dr. R. S. Stone with the delivery of 3,650 r. in air to each of three portals. (Calculated dose in the tumor, 5,058 r.) The mass decreased in size. The patient felt well and strong and returned to work, but his breasts continued to enlarge. Libido, potency and shaving habits remained normal. Data concerning weight, hemoglobin and blood pressure are summarized below.

DATE	WEIGHT *(pounds)*	HEMOGLOBIN *(gm.)*	BLOOD PRESSURE *mm. of mercury*
January 1942	168	12.2	135/85
August 1942	170		
March 1943	176	13.1	
January 1944	185		
January 1945	190		170/100
January 1946		15.9	
February 1946	180	13.9	170/100
April 1946	180	16.6	195/125
August 1946	197	17.4	230/130
January 1947			220/130
April 1947		18.1	220/140
May 1947	191	15.2	220/120



FIGURES 3 and 4.

It will be noted that over a period of five years the patient gained weight, his hemoglobin rose to polycythemic levels, and hypertension appeared. In February 1943, the patient had pneumonia and lost 20 pounds, but he quickly regained the lost weight. In September 1943, a rectal examination once more disclosed that the prostate was of normal size. In January 1945, it was found that the patient had hypertension. In January 1946, he had an episode of bleeding from his ulcer and lost a little weight, but regained it quickly on a bland diet. At this time an x-ray film of the chest (Figure 2) showed numerous dense masses in the lungs. It is of interest that the pulmonary masses were first detected in the course of a minifilm survey for tuberculosis at a time when the patient felt well and was working on a full schedule. X-ray therapy (approximately 800 r. in air through each of three portals) was delivered to a portion of the right side of the chest, but the masses progressed in size and number (Figure 3).

In April 1947, the patient complained of failing vision, headaches and dyspnea, and was found to have hypertensive retinitis with papilledema (Keith-Wagener IV). Examination again showed gynecomastia and normal-sized prostate and testes, but there was now a varicocele on the right side. The heart was enlarged to the left, the blood pressure was 220/120, and bilateral ankle edema was present. X-ray examination of the chest (Figure 4) showed progression in the number and size of the pulmonary masses.

The patient's symptoms were partially controlled by frequent lumbar punctures with reduction of the cerebrospinal pressure from 230 to 100 mm. of water. Assay of urinary 17-ketosteroids (ketonic fraction) showed an excretion of 224.5 mg. per day (10 times normal).

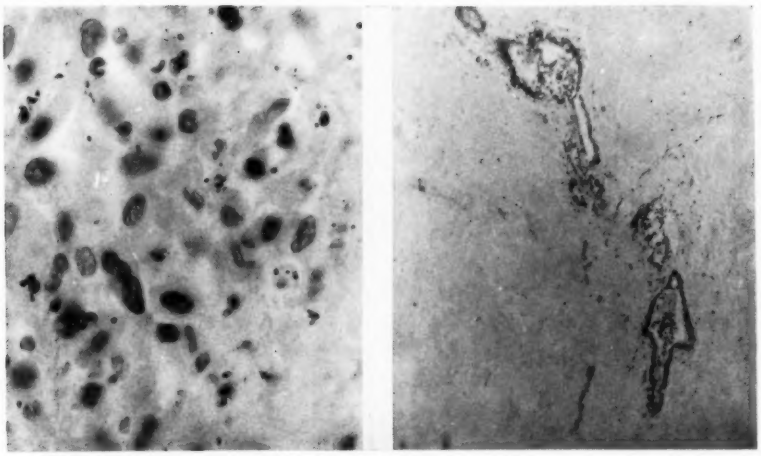
The patient continued to be active until October 1947, six years after the onset of symptoms, when he lapsed into coma and died.

Postmortem examination by Dr. J. F. McKenna—At autopsy, a large tumor was found arising from the right adrenal with extension to the right kidney and metastases to the liver, diaphragm and lungs. On histologic examination, the tumor cells were found to be large, with abundant pale, eosinophilic, granular cytoplasm (Figure 5). The right adrenal cortex had been completely replaced by the tumor mass. The left adrenal appeared normal and was not atrophic.

The breast enlargement was found to be associated with hypertrophy of the ductal system and especially of the periductal stroma (Figure 6). No acinar lobules were noted.

The testes were of normal size and histologically appeared well within normal limits. Spermatogenesis was seen to be in active progress (Figure 7). There was a slight increase in thickness of the basement membrane of the tubules and little, if any, reduction in number of the interstitial cells. The prostate was normal. The pituitary showed a moderate increase in eosinophils but was otherwise normal.

Hypertensive changes were found in the heart, blood vessels and brain. The right kidney had been compressed by the large tumor mass



FIGURES 5 and 6.

which had encroached upon the right renal artery and which had occluded the pelvis on that side. The right kidney was atrophic and histologically appeared ischemic with few erythrocytes in the glomerular capillaries (Figure 8). While the left kidney showed marked arterial and arteriolar subendothelial thickening, there was but moderate subintimal thickening of the smaller arteries in the right kidney. Scarring from a healed duodenal ulcer was identified.

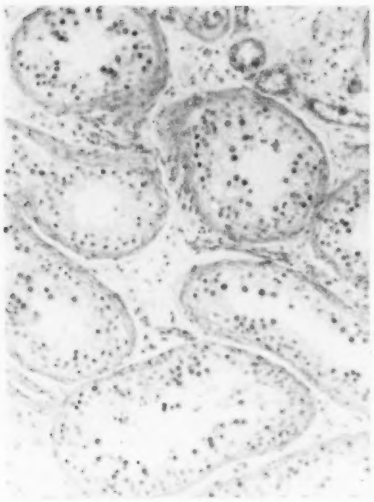
DISCUSSION

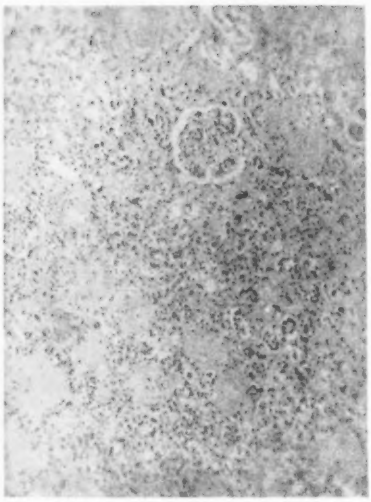
Adrenal cortical tumors may be nonendocrine in the sense that they cause no hormonal effects, or they may result in specific clinical syndromes determined by the type of hormone produced and the age and sex of the host.[14] Histologic examination of the tumor gives no clue to the type of hormone produced, if any. It is to be hoped that newer histochemical methods may improve this situation.[15] When endocrine effects are apparent, as Cahill has pointed out, they usually can be assessed as the effects of estrogens, androgens or corticoids ("11-oxysteroids") produced by the tumor.* The type of steroid present in excess may be determined by extraction of biologic fluids and chemical assay or bioassay in laboratory animals, or by clinical assessment of the effects of the hormone upon the patient, a "clinical bioassay."

The appearance of gynecomastia in our patient provides an interesting example of specificity (or nonspecificity?) of steroidal influence. Inasmuch as development of breasts is a feminine characteristic, gynecomastia has been regarded as evidence of "feminization." It is only when one attempts to appraise this abnormality as a manifestation of known effects of steroidal hormones that the complexity of the problem becomes apparent. Production of mammary growth has been reported in a number of species—including man—by estrogens,[18] androgens,[19] and desoxycorticosterone.[20] Nor does the histologic appearance of the breast aid greatly, for ductal, and particularly periductal, hypertrophy may be induced by testosterone as well as by estrogens.[21] It is therefore apparent that in this case the appearance of the breast provided no specific information whether the steroid produced in excess was estrogenic or androgenic.

In the testis, however, a different situation exists. The persistence of spermatogenesis is inconsistent with the production of large amounts of an estrogenic steroid. On the other hand, it has been shown repeatedly, contrary to widespread misconceptions, that testosterone is a potent stimulator of spermatogenesis *(vide infra)*. In this patient, from the appearance of the testis alone, one might suspect that the hormone produced was similar to testosterone and was not an estrogen. A number of other points strengthen this concept. The patient had maintained normal libido, potency and shaving habits, in contrast to the syndrome observed in patients with estrogen-producing tumors of the adrenal cortex.[22,23] The conclusion that the

*Recently, 2 cases of adrenal cortical tumors associated with the excretion of chorionic gonadotrophin have been reported, providing a further and still rarer classification.[16,17]





FIGURES 7 and 8.

steroid produced was similar to testosterone is further substantiated by the absence of cachexia despite multiple metastases, the lack of atrophy of the other adrenal, the absence of estrogenic metaplasia of the prostate, and the occurrence of polycythemia. This clinical impression is confirmed by the very high urinary 17-ketosteroid level, a phenomenon which cannot be assigned to the production of excess estrogenic steroids, inasmuch as estrogens are not excreted as 17-ketosteroids.

The hypertension is more difficult to interpret, since the ischemic right kidney provided a possible cause other than hormonal. It should be noted that the patient did not present the clinical appearance of Cushing's disease: no buffalo-type obesity, thin skin, striae, osteoporosis or glycosuria, or the contralateral adrenal atrophy or testicular damage commonly associated with excess of 11-oxycorticosteroids.

The knowledge of the effects of excessive testosterone in the adult male has been derived from the experimental administration of large amounts of testosterone to men as well as from observation of patients in whom large amounts of androgen are produced by an interstitial cell tumor of the testis. It is of some interest to compare such effects with the findings in our case.

The administration of large amounts of testosterone for long periods of time may produce many of the phenomena observed in this case. Weight gain is a constant anabolic feature associated with the administration of testosterone. Possibly this may explain why patients with numerous metastases from secreting tumors of the interstitial cells do not develop cachexia and have relatively long duration of life, as noted by Masson.[24] This significant characteristic of testosterone may prove useful in the treatment of debilitating diseases from other causes.

The maintenance of spermatogenesis with testosterone has been shown in the hypophysectomized rat by Walsh, Cuyler and McCullagh.[25] Simpson and Evans[26] not only confirmed the maintenance of spermatogenesis and normal mating behavior in hypophysectomized rats treated with testosterone but also their ability to sire a litter. A similar observation has been made in an hypogonadotrophic eunuchoid patient by Kinsell[27] and in normal young men by Beller and Turner.[28]

Administration of testosterone to young boys[29] occasionally leads to gynecomastia. The same effect may occur in old men and in eunuchoids.[30] As far as we know, the production of gynecomastia has not been reported in normal young adult men being treated with testosterone. We have, however, seen one patient, a 35 year old psychologist, who, following a course of psychoanalysis, felt unduly fatigued. This patient was treated elsewhere with 100 mg. of testosterone propionate twice weekly for two and one-half years, during which time he developed gynecomastia.

It has been postulated by Klinefelter, Reifenstein and Albright[31] that testosterone directly stimulates mammary development but is normally counterbalanced by a tubular secretion of the testis. This hypothesis would explain the occurrence of gynecomastia in young boys and old men as well as in eunuchoids treated with testosterone. Overdosage with testosterone in young adults might also produce gynecomastia if the amount were sufficient to overcome the hypothetical tubular secretion, as in the case of the psychologist already cited. As an alternative hypothesis, it might be postulated that the production of gynecomastia is not necessarily a direct effect, inasmuch as it has been shown that the administration of testosterone propionate results in increased excretion of estrogen in the urine.[32]

The induction of polycythemia with massive doses of testosterone propionate in patients with mammary carcinomatosis has been reported by Adair and others.[33]

Since the rise in 17-ketosteroid excretion in the urine after administration of testosterone propionate usually corresponds to about 40 per cent of the administered dose,[34] the theoretical production of testosterone-like steroids in this patient, who excreted 225 mg. of urinary 17-ketosteroids daily, might exceed 500 mg. per day.

A careful survey of the literature dealing with adrenal cortical tumors discloses two other cases, one reported by Armstrong and Simpson[35] and one by W. W. Scott,[36] in which a syndrome similar to that displayed by this patient was produced in an adult male by an adrenal cortical tumor. The case of Armstrong and Simpson was reported as an example of adrenal "feminism" because of the presence of gynecomastia. However, 17-ketosteroid excretion rose progressively to the fairly high level of 108 mg. per day, and there was no evidence of estrogenization of the testes. In their case the gynecomastia was associated not only with dilated ducts but also with "abundant glandular tissue producing a picture not unlike that of a female breast." It is, therefore, possible that this may have been an example of mixed androgenic and estrogenic production. In this respect, their case is similar to that of Roholm and Teilum.[37]

The case of W.W. Scott, described in a paper by Lawson Wilkins as an example of a "feminizing tumor," was that of a 43 year old man with gynecomastia, reduced libido and potency, normal hair and pigmentation, and abnormally high 17-ketosteroid excretion of 196 mg. per day. Analysis of the urinary steroids showed a large amount of dehydroisoandrosterone with no increase in estrogens. The case reported by Lisser[23] in 1936, but autopsied in 1925, might have been another instance of gynecomastia in an adult male due to an androgenic tumor of the adrenal cortex, since it was specifically mentioned that the luxuriant hirsutism of chest and abdomen had not been affected. Determinations of 17-ketosteroid excretion were not performed in 1925.

References cited in this article will be included in the authors' reprints.

SUCCESSFUL REMOVAL OF A BENIGN ANDROGENIC ADRENAL TUMOR FROM A DIABETIC WOMAN

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THE case to be narrated is commonly referred to as an example of "the adrenogenital syndrome." A more specific title, "androgenic," has been selected for this report because of a better understanding of an increasing variety of clinical manifestations produced by tumors of the adrenal cortex, depending not only upon the age and sex of the patient, but also more fundamentally attributable to the adrenal steroid responsible—in other words, a biochemical and a physiologic designation, rather than a cytologic one, since the microscopic picture may be indistinguishable. No attempt will be made to review the many excellent discussions regarding this and allied conditions which have appeared in the literature.

HAMILTON

SHEPARDSON

CASE REPORT

The patient, a 44 year old white woman, entered Franklin Hospital, San Francisco, on April 17, 1949, complaining of obesity, diabetes mellitus, amenorrhea and hypertrichosis.

Present illness—She originally was seen by one of us in 1926 because of obesity which had been present since the age of 12½ years. Menstruation had first appeared during her thirteenth year, and had recently become irregular. She weighed 213 pounds. Except for slight hypertrichosis of the upper lip, the hair distribution was normal. Blood pressure was 140/64; basal metabolic rate was 2 per cent plus. A weight reduction regimen was advised, but she failed to follow it.

She returned early in 1945, complaining that the hair on her head was falling out. She had not menstruated since 1937, but did not recall whether or not the amenorrhea was preceded by a period of hypomenorrhea. Her weight had increased to 240 pounds, and there was marked heterosexual hypertrichosis. Further study to determine the etiologic mechanisms involved was refused. In July 1945, she weighed 230 pounds and her blood pressure was 160/90. The basal metabolic rate was 16 per cent plus. X-ray films of the chest and an electrocardiogram were normal. The heterosexual hypertrichosis had increased.

Her office visits continued in an irregular

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fashion. In September 1946, her blood pressure was 140/90. X-ray examination of the skull and abdomen revealed no abnormalities. An oral glucose tolerance curve was considered borderline:

	Blood sugar
Fasting	100
½ hour	153
1 hour	182
2 hours	173
3 hours	111
4 hours	121
5 hours	83

She returned in April 1949, because of increasing baldness, polyuria, polydipsia, and increasing fatigability of a year's duration. The oral glucose tolerance test was repeated. The results confirmed the clinical impression of diabetes mellitus:

	Blood sugar
Fasting	246
½ hour	250
1 hour	285
2 hours	277
3 hours	273
4 hours	232
5 hours	243

The patient finally was convinced that hospitalization for complete evaluation of her case was essential.

Family history—Disclosed no evidence of endocrinopathy.

Marital history—Married twice. No pregnancies and no change in libido, which had always been normal.

Past history—Included the usual childhood diseases, but no serious illness. System review was essentially negative.

Physical examination—The patient was a woman who weighed 205 pounds, and was 65.5 inches in height. Her obesity was of the buffalo-type. There were numerous pale striae over the abdomen, on the upper arms and under the breasts. She spoke with a rather deep masculine voice. The patient had moderate alopecia, a heavy, closely shaven beard, and hypertrichosis involving chest, abdomen, back and extremities.

The blood pressure was 140/95 in both arms; the pulse, respiration and oral temperature were within normal limits. Examination of ears, nose, throat and eyes, including perimeter test for visual field defects and funduscopic examination, showed them to be normal. The thyroid was not enlarged. There was no lymphadenopathy. The breasts were pendulous, but otherwise were normal. The heart was not enlarged, and no cardiac murmurs were audible. The abdomen was moderately protuberant, nontender and devoid of palpable masses. There was definite enlargement of the clitoris and labia minora; neither the uterus nor adnexa were palpable by bimanual examination. The reflexes and peripheral vessels were within normal limits.

Laboratory examinations—The urine was normal except for glycosuria. A phenolsulfonphthalein excretion test revealed 35 per cent excretion during the first half-hour, and a total two hour excretion of 63 per cent. The blood count was normal, i.e., 14.7 gm. hemoglobin, 4.12 million red blood cells, and 5,450 white blood cells, with a normal differential. The fasting blood sugar was 191 mg. per cent. The following serum electrolyte values were obtained (given as millequivalents per liter): sodium, 141; potassium, 4.6; carbon dioxide, 27.5; chloride, 101.5; calcium, 5.5, and phosphorus, 2.3—all of which demonstrated a normal electrolyte balance. Serum proteins were 7.8 gm. per cent. The 17-ketosteroid assay was definitely abnormal, being 59.0 mg. per 24 hours. The basal metabolic rate was 18 per cent plus.

X-ray examination—There was no evidence of osteoporosis, the sella turcica was normal, and the petrous ridges smooth. The pineal body was calcified and in the midline. Intravenous pyelography revealed a shadow that suggested a mass over the upper pole of the right kidney. This impression was confirmed by injecting 400 cc. of carbon monoxide into the right perirenal space, following which x-ray revealed a large tumor mass, partially obscuring the superior pole of the right kidney.

It was concluded that the tumor should be removed surgically. During this period of investigation of the patient, the glycosuria had been fairly well controlled with 25 units of protamine zinc insulin administered daily before breakfast, and a diet containing 1,970 calories (carbohydrate, 180 gm.; protein, 110 gm., and fat, 90 gm.). During the immediate preoperative and postoperative phase, in order to facilitate control of the diabetes mellitus, crystalline insulin was given before meals in amounts indicated by the degree of glycosuria.

Because of the possibility of adrenal cortical insufficiency during the immediate postopera-

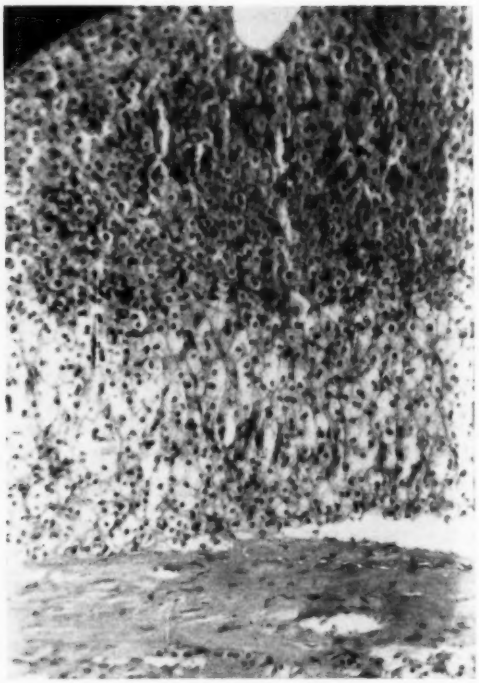

FIGURE 1. A section of the adrenal adenoma demonstrating an intact capsule and a middle layer, the zona fasciculata, which consists of polyhedral cells with vacuolated cytoplasm due to the loss of the lipoid elements in preparation of the tissue. The lower half of the photomicrograph shows cells which differ little from the zona fasciculata except for decreased vacuolization of the cytoplasm, and which represent the normal zona reticularis.

tive phase, 20 mg. of desoxycorticosterone acetate was administered intramuscularly three times daily during the 72 hours preceding surgery. Before the patient was sent to operation, 10 mg. of desoxycorticosterone acetate and 15 cc. of purified whole adrenal extract were injected intramuscularly. During the surgical procedure, her blood pressure remained constant at the preoperative level of 120/70. At operation, the tumor mass was found to be well encapsulated and hence readily mobilized. After removal of the tumor from its very small pedicle, the subsequent bleeding was easily controlled. It was assumed that the right adrenal gland was incorporated in the tumor mass, as exploration of the area failed to reveal additional adrenal tissue.

The tumor was 8 cm. in diameter, burnt orange in color, and relatively smooth. Microscopic examination revealed cells similar to those seen in the zona fasciculata and the zona reticularis of the normal adrenal (Figure 1). The adrenal tissue was partially replaced by fat; there were large cystic areas of degeneration. The cells were uniform in size and in staining property. Small areas of interstitial hemorrhage were present; there were many macrophages filled with a brown staining pigment. There was no evidence of malignancy. The pathologic diagnosis was adrenal adenoma.

POSTOPERATIVE PERIOD

The postoperative course was uneventful. Thirty cubic centimeters of purified extract of whole adrenal cortex was administered in divided doses during the first 18 postoperative hours and 10 cc. was given on the second postoperative day.

Ten days after removal of the adenoma, a 17-ketosteroid assay revealed 9.7 mg. per 24 hours. The blood pressure remained constant at 130/80; the basal metabolic rate was 18 per cent plus. There was no change in electrolyte balance. The postoperative fasting blood sugar was 210 mg. per cent. The patient weighed 193 pounds.

The pattern of the diabetes mellitus did not change. The patient continued to be well controlled with the same diet and insulin dosage that was utilized during the preoperative phase.

The patient was operated upon May 5, 1949. On June 7, 1949, menstruation occurred for the first time since January 1937. This was a normal period of five days' duration. A second normal period occurred August 14, 1949. Thereafter followed a period of amenorrhea which extended to April 1950. Since the latter date menstruation has occurred, with only slight variation, at monthly intervals. The hair of her scalp is more luxuriant, and it would appear that her alopecia is subsiding. The hypertrichosis of the face and extremities, which necessitates daily shaving, has not altered noticeably, but the hair of the body seems to be involuting. Her weight has not changed appreciably, but her voice is less masculine.

DISCUSSION

With the exception of the buffalo-type obesity suggestive of Cushing's syndrome, this patient presented all of the characteristics

of the adrenogenital syndrome as outlined by Kenyon.[1] Whether she is representative of Kenyon's Group 3 (a mixture of the adrenogenital and Cushing's syndrome) is not a matter of great importance.

It seems unlikely that the diabetes mellitus present in this case represented a dysfunction secondary to the adrenal adenoma—*diabète des femmes à barbe* (Archard-Thiers syndrome)[2]—but rather was purely coincidental. Most assuredly, the ease with which the condition was controlled marks it as quite different from the "steroid diabetes" associated with Cushing's syndrome, recently described by Sprague and associates,[3] which is usually quite resistant to insulin. Furthermore, removal of the tumor had no favorable influence on the diabetes, a fact which suggests that the disturbance in adrenal function was not a morbific factor in the development of the disease.

It is not surprising that the hypertrichosis of the previously shaved areas failed to change postoperatively, for this frequently occurs under such circumstances. The involution of hair in the unshaven areas, associated with the feminization of voice and a significant drop in the 17-ketosteroid level, certainly suggests that the adenoma was responsible for the virilization that occurred.

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PHEOCHROMOCYTOMA: REPORT OF A CASE WITH SYMPTOMS SIMULATING ACUTE ANXIETY ATTACKS

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Symptoms produced by a pheochromocytoma and those associated with acute anxiety are often similar. The following case report indicates the need for a thorough investigation, utilizing all available clinical, laboratory and pharmacologic technics, of any patient who presents a history of paroxysmal symptoms suggesting acute anxiety attacks.

G. S., a white, married truck driver, was 43 years old when first seen in the University of California Medical Clinic in January 1944. He had noted the sudden onset of "nervous spells and headaches" about one year before. These symptoms had persisted and increased in frequency and severity. They were frequently precipitated by exertion and would occur when he bent over to attach hoses on his gasoline truck. He described a typical attack as beginning suddenly with a feeling of nervousness, trembling, fullness and pounding in the neck and head, sweating, hard breathing, and a forceful heart beat. These symptoms, which persisted from 30 to 45 minutes, were followed by extreme weakness. In the previous three months the attacks had been followed by generalized "splitting, pounding" headaches, which lasted two to three hours. At the time of his first visit to the clinic, the attacks were occurring two to four times a day. The remainder of the history was not significant.

Although the physical examination revealed no abnormalities, the patient was hospitalized to investigate the possibility of a pheochromocytoma. While in the hospital his blood pressure varied from 120/70 to 150/88. No attacks were observed, although after three minutes of hyperventilation the patient stated that he felt the beginning symptoms—a "jittery feeling," mild headache, and "pounding of his heart." He became somewhat pale, his blood pressure rose to 160/96 with a pulse rate of 60 a minute. Massage of either flank, flexion of the trunk, and a cold pressor test failed to precipitate an attack. Urinalysis, blood Wassermann, electrocardiogram and five hour glucose tolerance test were within normal limits. One blood count, which was not repeated, revealed a mild anemia (hemoglobin, 12.1 gm., 83 per cent; red blood cells, 4.04 million). A plain x-ray film of the abdomen was read as being normal.

CREDE

After the patient had been under observation in the hospital for four days, it was believed there was no definite evidence to support the diagnosis of pheochromocytoma and that symptoms were due to acute anxiety attacks. He was referred to the Psychiatric Clinic but did not return after his initial interview.

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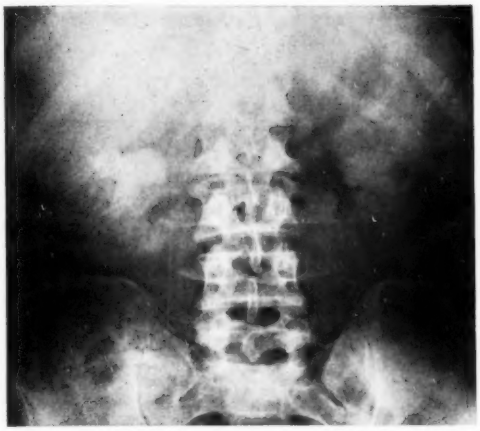

FIGURE 1. Intravenous pyelogram; film taken in upright position 40 minutes after dye was injected. The right renal pelvis and calyces still contain opaque medium and appear dilated. The upper major calyx is not seen. There appears to be a soft tissue mass superior to the right kidney.

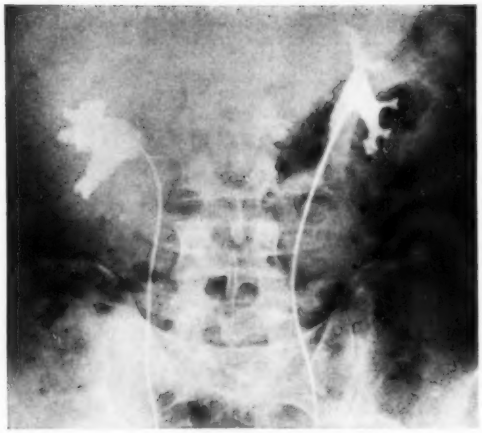

FIGURE 2. Retrograde pyelogram. The right kidney is displaced downward and there is distortion of the calyces due to pressure from a suprarenal mass.

Approximately three years later, in December 1946, the patient returned to the Medical Clinic with a letter from Dr. H. P. Struble of Hayward, California, asking that we re-evaluate the patient. During the three year interval, the attacks had increased in frequency and severity, forcing the patient to abandon truck driving and seek easier work. Recently, he had to stop work altogether because of the frequency of the attacks and his increasing fatigability. He had lost 10 pounds of weight since his previous visit. Dr. Struble had observed the patient during two spontaneous attacks characterized by the sudden onset of a cyanotic appearance of the neck and face, a rise of blood pressure from 150/90 to 250/110, accompanied by a slow, bounding pulse. These attacks lasted about three minutes, after which the blood pressure gradually returned to the pre-attack level. Because of this objective evidence, Dr. Struble suspected that the patient had an adrenal medullary tumor.

The patient was re-admitted to the University of California Hospital on January 22, 1947. Physical examination revealed suffusion of the neck, face and oral mucous membranes. There was moderate generalized narrowing of the retinal arterioles with some areas of localized narrowing but no definite evidence of sclerotic changes. The optic disks were normal and no hemorrhage or exudate was seen. The heart was not enlarged and no significant murmurs were heard. The peripheral vessels appeared normal, and strong pulsations were felt in the femoral and pedal arteries. No abdominal masses were palpable and neither massage of the flanks nor flexion of the trunk precipitated typical attacks. The blood pressure varied from 130/85 to 230/100, with the majority of readings around 150/90. Three spontaneous attacks were observed, during which the blood pressure reached a peak of 250/130 and fell to 170/100 within 12 minutes. At the onset of the attack the patient's face and hands were pale and the pulse slow and bounding; later he appeared flushed and the pulse rate increased to about 100 a minute.

THE presence of a right suprarenal mass was suggested by intravenous pyelography (Figure 1) and confirmed by retrograde studies (Figure 2). The latter procedure precipitated a typical attack. X-ray examination of the skull revealed no abnormalities. X-ray films of the chest showed the heart size to be at the upper limits of normal. The electrocardiogram was characteristic of left ventricular hypertrophy with associated coronary artery disease.

The values for red blood cell count, hemoglobin and packed cell volume were at the upper limits of normal, and cytologic examination of the bone marrow revealed a definite shift to the left of the myeloid series. The sedimentation rate was within normal limits.

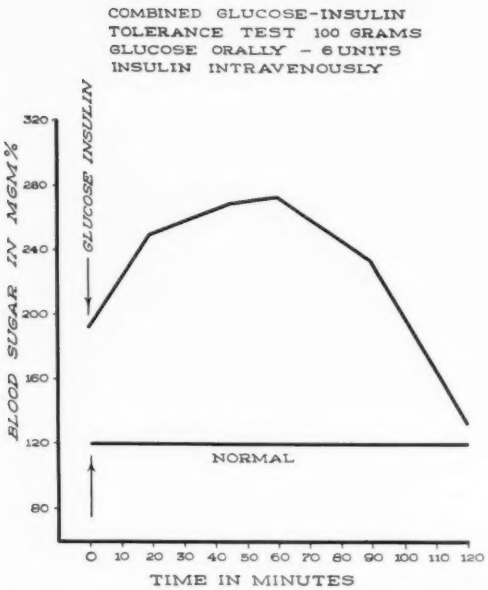

FIGURE 3. Combined glucose-insulin tolerance test: 100 gm. glucose orally, 6 units insulin intravenously.

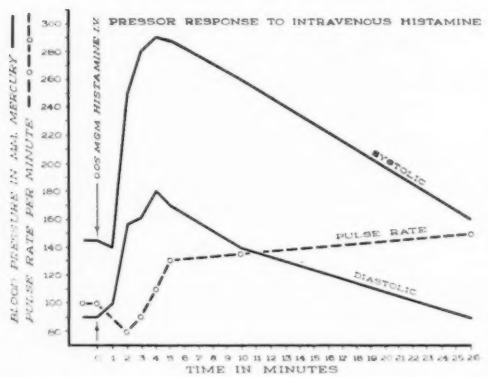

FIGURE 4.

Random urinalyses revealed green-yellow reduction, albuminuria and abnormal numbers of red blood cells, white blood cells and casts. Addis count values were: 1.2 gm. protein per liter; specific gravity, 1,029; 10,500,000 casts (all hyaline); 10 million red blood cells and 1.7 million white blood cells. Phenolsulfonphthalein excretion was impaired (10 per cent in 15 minutes, total of 55 per cent in one hour) and the urea clearance was 51 per cent of normal. The blood nonprotein nitrogen was 39 mg. per cent.

The fasting blood sugar was 190 mg. per cent (normal 90 to 120 mg. per cent) and the standard glucose-insulin tolerance test[1] was abnormal (Figure 3). The patient had spontaneous attacks 12 hours before and three hours after this test was performed. This might explain the high fasting blood sugar and the increased hyperglycemia 60 minutes after the test was begun. Liver function, as measured by proprietary dye excretion, was normal.

Twenty-four hour urinary 17-ketosteroid excretion was low (7.2 mg. ketonic); the normal range for males in our laboratory is 10.7 to 20.6 mg. Blood calcium, phosphorus, sodium, potassium and alkaline phosphatase were within normal limits.

In an attempt to produce a typical paroxysm several tests were carried out. An intravenous injection of insulin (6 units) reduced the blood sugar from 143 to 58 mg. per cent but did not produce an attack. As in the first entry the patient's response to a cold pressor test was normal. However, the intravenous injection of 0.05 mg. of histamine precipitated a typical attack with an immediate increase in blood pressure from 145/90 to 290/180 (Figure 4).

Our observation of spontaneous and histamine-induced attacks with the presence of a right suprarenal mass established the diagnosis of pheochromocytoma.

The patient was taken to surgery on February 1, 1947. Dr. Clark Johnson and Dr. Frank Hinman, Jr. removed a large right adrenal tumor, measuring 12 by 10 by 9 cm. and weighing 490 gm. (Figure 5). Pathologic examination revealed the tumor, which was surrounded by a tough fibrous capsule, to consist of homogenous tissue with a greyish red, meaty appearance (Figure 6). There were numerous cystic areas which contained about 200 cc. of a serosanguineous fluid. The microscopic report stated: "The tumor is composed of large polyhedral, pleomorphic cells with abundant granular, basophilic cytoplasm. These are generally arranged in solid sheets but occasional irregular cords and follicular formations are seen. Mitotic figures are rare and there is no invasion of the capsule. Special fixation revealed that a majority of these cells give a positive dichromate reaction. Infrequent large, eosinophilic cells with three or four coarsely granular nuclei are seen and are thought to be ganglion cells. A portion of attached ad-

FIGURE 5. Gross appearance of tumor. Scale in centimeters.

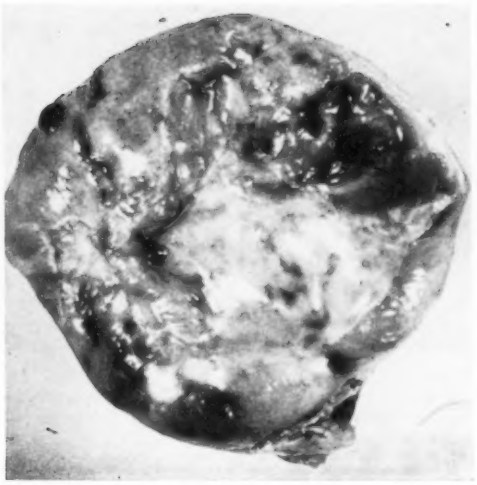

FIGURE 6. Cross section of tumor.

renal cortex is normal. Diagnosis: pheochromocytoma." (Figure 7.)

During the operative procedure and prior to removal of the tumor, the systolic blood pressure rose over the 300 level. A precipitous drop in pressure, to 80 mm. systolic, occurred after removal of the tumor, but a satisfactory level was maintained by the intravenous and subcutaneous administration of epinephrine combined with intravenous plasma, blood and normal saline solution.

During operation and in the subsequent 12 hours the patient received a total of 22 mg. epinephrine (16 mg. by continuous intravenous infusion, 3 mg. by subcutaneous and 3 mg. in oil by intramuscular injection). During this period the patient was given 2000 cc. plasma, 500 cc. whole blood, 1000 cc. normal saline solution, 1000 cc. 5 per cent glucose in water, and 1500 cc. 10 per cent glucose in water. In the next 24 hours (first postoperative day), he was given 9 mg. epinephrine subcutaneously and 14 mg. epinephrine in oil intramuscularly. This dosage maintained the blood pressure at 100 to 120 systolic and 60 to 70 diastolic.

During the second and third postoperative days the patient received 24 mg. of epinephrine in oil by intramuscular injection. By the fourth postoperative day the blood pressure had stabilized at approximately 130/80. The packed cell volume dropped from 50 to 25 cc. per cent within 36 hours after surgery. The subsequent postoperative course was complicated by the development of atelectasis and pneumonitis, and the patient required five 500 cc. transfusions of whole blood in the first week after the operation. There was no significant disturbance in electrolyte equilibrium in the postoperative period. The patient was discharged on the eighteenth day after operation, at which time his blood pressure was averaging about 140/80.

We have not examined the patient since his discharge from the hospital, but Dr. Struble states that the patient is asymptomatic and was able to resume his former occupation within two months after he left the hospital.

DISCUSSION

The symptoms and signs of sympathetic autonomic overactivity associated with acute anxiety may be identical with those caused by periodic epinephrine secretion from an adrenal medullary tumor. The possibility of a pheochromocytoma should be considered in any patient who presents a history of paroxysmal episodes suggesting acute anxiety attacks, particularly when the physiologic disturbances are very severe.

The early diagnosis of pheochromocytoma is imperative, as prompt surgical removal of the tumor has been followed by a cure in approximately 85 per cent of patients reported in the literature since 1936.[2] As an aid to establishing

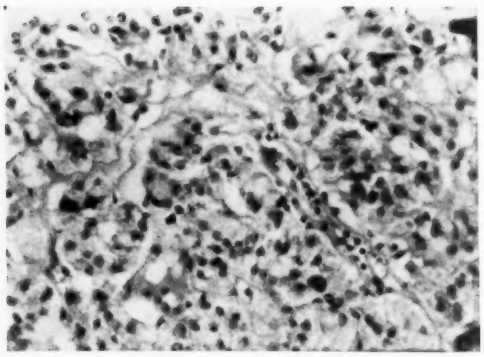

FIGURE 7. Photomicrograph (320 x) of tumor. The chromaffin tumor cells have abundant cytoplasm and lightly staining nuclei. Occasional "pseudofollicular" formations are seen.

(Photomicrograph, courtesy of Dr. Elizabeth Lowenhaupt, Division of Pathology.)

a diagnosis, numerous pharmacologic tests have been suggested. The use of acetyl-beta-methylcholine (MECHOLYL®),[3] tetraethylammonium bromide[4] and histamine[5] to precipitate paroxysms of hypertension has been described.

Histamine has produced a great rise in blood pressure in all reported cases of proved pheochromocytoma when the test was performed in a normotensive period. Histamine may fail to cause a significant rise in blood pressure in patients who have persistent hypertension due to a pheochromocytoma. Hypertensive responses to histamine have been described in patients without pheochromocytoma.[3-6] This emphasizes the fact that a hypertensive response to histamine is not diagnostic of a pheochromocytoma. The limitations and dangers of the histamine test have been reported by Cahill[6] and Smithwick.[7]

Various adrenolytic agents, such as piperidylmethyl-benzodioxane (933-F),[8] DIBENAMINE®[9] and C-7337 (an imidazoline derivative),[10] have been used to discover persistent hypertension due to circulating epinephrine. Benzodioxane, in rare cases, may cause a hypotensive response in the absence of a pheochromocytoma[11,12] and may produce untoward side effects in patients with essential hypertension.[13] Although these pharmacologic tests may be of value in establishing the diagnosis of pheochromocytoma, they should be used with caution and a full recognition of the risks involved.

Although we considered the possibility of a pheochromocytoma when this patient was first seen in our clinic, he had no paroxysms while under observation. The use of histamine as a provocative test[5] had not as yet been described. The erroneous diagnosis of acute anxiety with hyperventilation was made by the "exclusion method," which is poor medical practice. Psychiatric assistance during this first study might have led us to the correct diagnosis by demonstrating the absence of any underlying emotional disturbance which might produce acute anxiety.

In the three years before he returned to our clinic, the patient had sought relief from numerous physicians before the correct diagnosis was established. During this period he developed vascular disease with evidence of myocardial and renal impairment, as well as disturbance in carbohydrate metabolism.

On his second admission to the hospital, we observed several spontaneous attacks which were of diagnostic value. At the onset of an attack, the patient had a slow, bounding pulse which was due to reflex cardiac inhibition, secondary to the abrupt rise in blood pressure. A minute or two later the heart rate would increase, presumably due to the direct action of epinephrine on the heart. A similar sequence of events was noted during the histamine-induced attack.

The hyperglycemia, glycosuria and abnormal results of the glucose-insulin tolerance test can be explained by the excessive glycogenolysis resulting from increased epinephrine secretion. However, we cannot rule out the possibility that adrenal cortical hyperfunction, secondary to epinephrine stimulation of the anterior pituitary, may have contributed to these abnormalities.[14,15] Although the 17-ketosteroid excretion was below normal, the absence of postoperative disturbances in electrolyte metabolism suggests that this phase of adrenal cortical function was adequate.

THE large amounts of epinephrine needed to stabilize the blood pressure following removal of the tumor and in the immediate postoperative period are not unusual and have been described by other authors.[11,16,17] It is obvious that significant alterations in the capacity of the vascular system will occur when the source of an excess vasoconstricting agent is removed. With adequate adrenal cortical function, the parenteral administration of epinephrine com-

bined with blood, plasma and other intravenous fluids will maintain a satisfactory balance between vascular capacity and circulating blood volume. The moderate anemia observed in the postoperative period may reflect the rapid increase in blood volume necessary to maintain circulatory function. Engel[18] has described similar circulatory dysfunction following a prolonged spontaneous attack in a patient with a pheochromocytoma.

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"Surfeyte, age, and sickenes, are enemyes all to health,
Medicines to mende the body, excell all worldly wealth;
Pisicke, shall florishe, and in daunger will give cure,
Till death unknit the lively knot, no longer wee endure."

From "The Booke of the Use of Sicke Men and Medicines," by William Bullein (1579).

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RENAL CYST SIMULATING PHEOCHROMOCYTOMA

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SYMPTOMS of pheochromocytoma are so nonspecific that they may be mimicked by disorders as different as essential hypertension or an acute anxiety state. On one hand, we recently removed a pheochromocytoma from a patient in whom the latter diagnosis had been made, as described by Crede and Kerr,[1] while, on the other hand, we now report on a man with symptoms, as well as certain signs, of pheochromocytoma who subsequently proved to have recurrent states of acute anxiety.

In essence, our present case deals with a remarkable triple coincidence: (1) attacks suggestive, if not typical, of sympathetic discharge, (2) a mass in the suprarenal area, and (3) hyperreaction to histamine.

CASE REPORT

Since 1948, the patient, a 48 year old, single, male artist, had had recurrent attacks of severe palpitation, with trembling, most noticeable in the hands, cold feet and marked weakness. There were no aftereffects except weakness. These episodes recurred at irregular intervals with varying severity and duration, but appeared to be increasing in frequency. An attack would last from a few minutes to as long as eight hours. The patient did not know whether his skin blanched or if his pupils became dilated. He had some sweating of the feet during attacks, but no sweating was noticed in the palms of the hands or elsewhere. There was no associated syncope, vertigo, vomiting or headache. He believed the palpitation was accompanied by an increase in heart rate. Although there was no known precipitating factor, the patient found that the attacks often started after a day of hard physical labor, usually after supper. During this period he had not lost weight nor experienced fever. He stated that cancer was prevalent in his family.

During puberty, the patient had had bilateral mumps orchitis with subsequent testicular atrophy. Secondary sex characteristics developed normally, but the patient was chronically impotent, except when taking testosterone.

All his life the patient had had periods of severe depression with feelings of inadequacy. Shortly before the onset of his paroxysmal episodes, he had moved to an isolated area where he worked alone, sometimes not seeing friends for days. While he was concerned about his attacks, he felt that, on the basis of his emotional background and loneliness, he had no need for medical care. In April 1950, however, he had

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an attack of such severity that he sought medical help.

Following the medical examination, an intravenous pyelogram was made, which was interpreted as showing a tumor in the left suprarenal area (Figure 1). This led to admission of the patient to the University of California Hospital for further study.

Physical examination revealed an asthenic but otherwise normal male habitus. Blood pressure was 130/90 mm. of mercury, and the pulse rate was 86. During his preoperative hospital stay, day and night blood pressure recordings ranged from 105/65 to 148/90, and pulse rates varied from 68 to 92. There was no exophthalmos. The thyroid gland was not enlarged. The heart borders were normal and the sounds of good quality. There were no murmurs nor arrhythmias and the heart was not enlarged. There was no tenderness in the abdomen and no masses could be felt. Massage of both flanks would not precipitate an attack. Bilaterally atrophic testes was the only other physical finding of note.

During preoperative study, the patient developed an attack similar to those he had described. This was the first to be observed by a physician. His hands trembled, his respirations were rapid and his feet were cold. His pupils were not dilated and the palms of his hands were not particularly cold or sweaty. His blood pressure remained at 112/76 and the pulse rate at 80, without evident arrhythmia. The episode lasted about two hours, and in the observer's opinion was an acute anxiety attack.

The cold pressor test produced no significant rise in blood pressure. The histamine test,[2] which was done on two occasions, once with 0.05 mg. and again with 0.1 mg. of histamine base administered intravenously, resulted in a rise of blood pressure to 172/112 mm. of mercury in two minutes, following an initial drop to 90/48; in 45 minutes, the blood pressure was back to basal levels (Figure 2). To contradict this positive evidence was the fact that 500 mg. of tetraethylammonium chloride[3] given intravenously failed to cause a significant rise in blood pressure. In addition, the response to the insulin tolerance test was normal.

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Laboratory studies gave essentially normal results, except for a reduced number of circulating eosinophils, 43 per cubic millimeter (normal, 60 to 400). Results of urinalysis and an oral glucose tolerance test, the blood count, and the levels of sodium, potassium, chloride, carbon dioxide-combining power, and nonprotein nitrogen in the serum were all normal. Excretion of pituitary gonadotrophin was normal (positive at 5 m.u. per 24 hours), and 17-ketosteroid assay (total neutral steroid) also was normal (22 mg. per 24 hours). Two electrocardiograms and a chest x-ray were normal.

Ureteral catheterization revealed good function bilaterally, without infection. Retrograde pyelograms again defined the mass over the left kidney which distorted the upper renal calices, but to a lesser degree than that shown in the intravenous urograms.

ALTERNATIVE preoperative diagnoses were adrenal tumor (? invading kidney), renal neoplasm or renal cyst. It was our opinion that a pheochromocytoma had not been ruled out definitely and, therefore, preparations were made for handling possible critical hypotension following removal of such a tumor. Two large needles (one, a cannula inserted by direct cutdown into a vein) were placed so that fluid and blood could be administered rapidly and dilute epinephrine and cortical extract also could be given if needed.

A transverse upper abdominal incision was chosen to allow direct approach to the adrenal area with minimal manipulation. The left suprarenal area was easily reached, and a simple cyst, 10 cm. in diameter, was seen, which arose from and indented the upper pole of the kidney. The adrenal gland was exposed, examined and considered normal. The cyst was excised and, after closure of the wound, the patient was returned to the ward without incident.

Postoperatively, the patient showed a satisfactory convalescence. Subsequent therapy consisted of management of his anxiety state.

FIGURE 1. Pyelogram showing the outline of a tumor at the upper pole of the left kidney deforming the calices and pushing them downward and laterally.

DISCUSSION

Prior to the operation there had been a difference of opinion regarding the diagnosis. The history was not entirely typical of pheochromocytoma, the symptoms resembling more closely those of an anxiety state. While the histamine test was suggestive of pheochromocytoma, the blood pressure rise was not as great as would be expected in this condition. The failure of the blood pressure to rise significantly following administration of tetraethylammonium chloride was added evidence against the diagnosis of pheochromocytoma. Observation of the patient during a typical attack, in which there was hyperventilation and trembling, but no rise in blood pressure or pulse, further diminished the likelihood of this diagnosis. Since, however, the clinical history suggested the possibility of pheochromocytoma and a tumor was present in the location of the left adrenal gland, it was generally agreed that precautionary preparation should be made for dealing with a pheochromocytoma at the time of surgery.

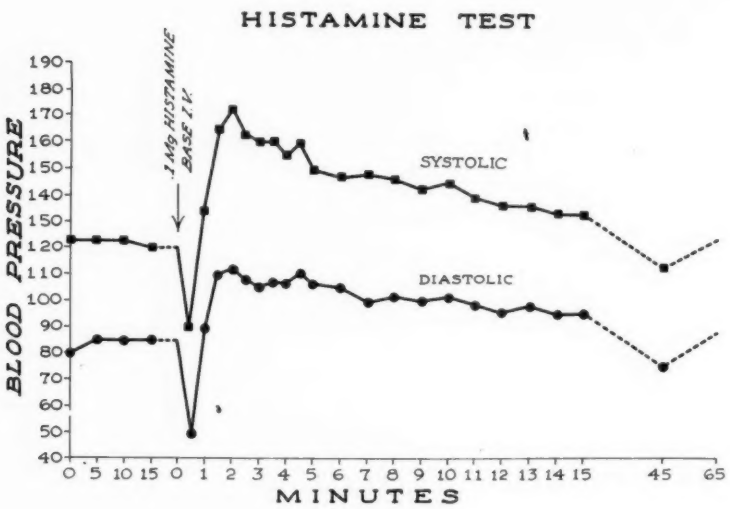

FIGURE 2. Blood pressure determinations following intravenous administration of histamine.

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LARGE ADRENAL CYSTIC TUMOR WITHOUT ENDOCRINE MANIFESTATIONS

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Cysts of the adrenal gland are of rare occurrence. The first case, mentioned by Terrier and Lecène[1] in a review of the literature, was that described by Rayer in 1837. These authors found 9 authenticated instances up to 1906 and added 1 of their own. Since that time additional cases have been reported every few years. Terrier and Lecène classify them into five categories: cystic lymphangiomas, pseudocysts, parasitic (hydatid) cysts, true glandular (retention) cysts and cystic adenomas. Of these, the last three are of extreme rarity; the first two types appear to account for the majority of cases and each may attain a large size. Hartwell[2] reported a cystic lymphangioma containing 3 quarts of fluid; Bourcy and Legueu,[3] one containing 5 liters, and Pawlik,[4] one containing 10 liters. Pseudocysts arise from either hemorrhage into, or necrosis of normal or abnormal glandular tissue. Henschen[5] reported a case of this type in which the cyst measured 26 by 16 by 14 cm.

Characteristically the symptoms of a large adrenal cyst are vague and nonspecific. Unless bleeding occurs, the cyst grows slowly and insidiously, displacing the diaphragm and abdominal viscera so gradually that it is usually first noticed by becoming palpable beneath one or the other of the costal margins. Since the large cysts are always unilateral, there is no associated adrenal insufficiency. They occasionally cause sacral or pleural pain and this, in conjunction with the vomiting which may occur, may suggest a gastric crisis.

There are other abdominal cysts which, on rare occasions, may reach large proportions and should, therefore, be considered in the differential diagnosis of a case such as the present one. Among these conditions are cysts of the liver (parasitic and nonparasitic), distention of the gallbladder, cystic dilatation of the common bile duct, and cysts of the urachus, kidney, pancreas and mesentery. Some reported examples of these are the following: a nonparasitic cyst of the liver containing 12 liters of fluid;[6] a dilated gallbladder containing about 60 pounds of fluid;[7] a cyst of the common bile duct, nearly 8 pints;[8]

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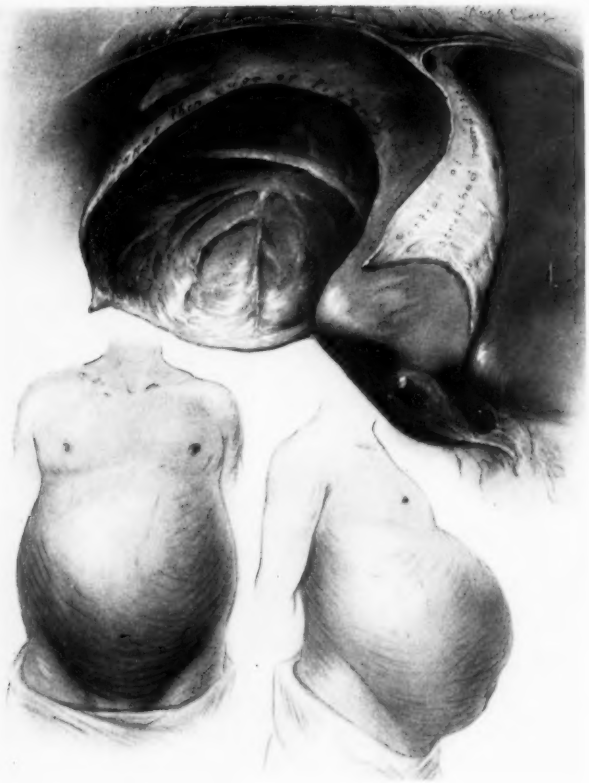

FIGURE 1. View of patient before surgery. Upper view shows the depression made in the right lobe of the liver and dislocation of the gallbladder to the left upper quadrant.

a urachal cyst, 6 quarts;[9] a renal cyst, 10 liters;[10] a pancreatic cyst, 15 liters;[11] and a mesenteric cyst, 8 quarts.[12]

The surgical risk entailed in removing such large cysts is considerable, all the fatalities reported in the literature having been attributable either to shock or to peritonitis; but once the cyst has been successfully removed, the results have been excellent. The ideal treatment is complete extirpation. If this is not feasible, the cyst may be opened and drained or marsupialized. To deliver the cyst it is necessary to collapse it, but this must be undertaken with caution to avoid too sudden lowering of intra-abdominal pressure. Adequate amounts of blood and other fluids should be available for intravenous administration in order to combat shock during the operation.

The present case is of interest because of the rarity of such cysts and the size the cyst had reached before surgical intervention.

CASE REPORT

K. L. M., a 54 year old white plumber, entered the University of California Hospital on November 5, 1948, with a chief complaint of enlargement of the abdomen over a period of about four years. Despite an average daily intake of approximately one quart of whiskey for some 20 years, he had been in good health until about two and one-half years previously. At that time he began to have nausea and vomiting almost every morning after breakfast, which was finally relieved by abstinence from liquor and by eating a small breakfast. He had done very little drinking since that time. About one and one-half years before admission, he was struck in the abdomen by the tail gate of a truck. This caused a severe, deep, aching periumbilical pain, lasting several days and requiring morphine for relief. He believed his abdomen had enlarged more rapidly following this accident and that he might have been jaundiced for a time. His only other symptoms during these four years were flatulence, relieved by belching and the passage of flatus, distress on eating a large meal, and the loss of about 10 pounds in weight; he had never been troubled by constipation or symptoms referable to the urinary tract.

His referring physician considered him to have cirrhosis of the liver with minimal ascites and had been treating him accordingly. Paracentesis was not done. Because of failure to improve, he was referred to one of us (T. L. A.).

SIGNIFICANT physical findings were limited to the chest and abdomen. Respiratory excursion was markedly limited and the leaves of the diaphragm were elevated to the third interspace. The apex of the heart was in the third interspace at the left anterior axillary line. On the surface of the abdomen there were numerous dilated vessels in which blood flow was away from the umbilicus. An appendectomy scar was noted in the right lower quadrant. The

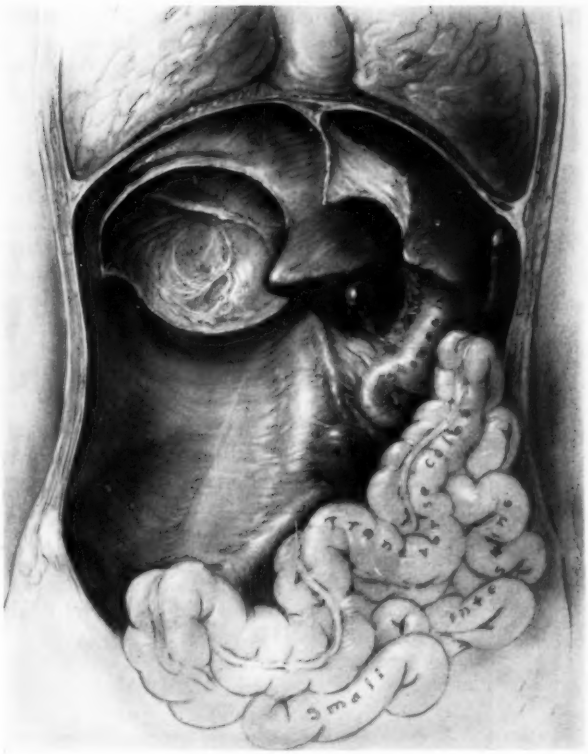

FIGURE 2. View inside abdomen after removal of the cyst. Note position of right kidney.

abdomen was hugely distended (Figure 1), with a rounded, smooth, firm mass filling it completely except for the left lower quadrant, and it was dull on percussion everywhere except in the left lower quadrant where the sound was tympanitic. A plain x-ray film of the abdomen showed only a tremendous soft-tissue mass anterior to the spine, with its center approximately opposite the second lumbar vertebra. Its lower border was smoothly rounded. The rest of the mass could not be penetrated in spite of the fact that the film was made at tube limit. Roentgenograms of the gastrointestinal tract showed all structures displaced to the left and downward into the left lower quadrant.

With the exception of the BROMSULFALEIN® test, a series of liver function tests gave results within normal limits: thymol turbidity was 5 units; alkaline phosphatase was 4 units; icterus index was 6 units; cephalin cholesterol flocculation test was negative after 24 hours and two plus after 48 hours; the bromsulfalein concentration in the blood was 12 per cent after 45 minutes and 6 per cent after 60 minutes. Routine blood count showed 15.4 gm. of hemoglobin, 5.23 million red cells, 8100 white cells, 67 per cent neutrophils and 23 per cent lymphocytes. Corrected sedimentation rate was 1 mm. in an hour by the Wintrobe method. On the basis of these tests, cirrhosis of the liver and other generalized diseases of the liver were considered to be ruled out and the patient was referred to H. G. B. for exploratory laparotomy.

Under local anesthesia a small right rectus incision was made down through the peritoneum. A cystic mass was revealed, which was free from peritoneal attachments anteriorly and had a smooth, reddish brown surface over which there was a lacework of dilated blood vessels. The cyst was partly collapsed by aspiration of about 8 liters of turbid, brownish fluid through a trocar. Because the patient's systolic blood pressure repeatedly fell to the neighborhood of 80 mm. of mercury, it was necessary to interrupt this procedure several times. The patient was then anesthetized with nitrous oxide and the incision enlarged into the shape of a T by extending it upward, downward and to the right. Exploration through this extensive incision revealed that the cyst was retroperitoneal and was covered anteriorly by the gastrocolic ligament. It had displaced the diaphragm upward to about the third interspace. The liver was pushed upward and to the left, the gallbladder and spleen were high under the left costal margin, and the stomach was far to the left of its normal position. The transverse colon, small bowel and right kidney were in the left lower quadrant.

In order to deliver the cyst, it was necessary to cut through the peritoneum in the right paracolic gutter, as well as to sever the gastrocolic ligament. A large vein was seen running from the left upper pole of the cyst to the inferior vena cava. At the time of the operation it was impossible to tell whether this was the

right renal or right adrenal vein. After ligation of this vein, the cyst was separated from where it had buried itself into the right antero-inferior surface of the liver (Figure 2) and was lifted out of the abdomen.

After removal of the cyst, it was interesting to see how rapidly the abdominal organs tended to resume their normal positions. Before closure of the incision, the kidney had moved from the left lower quadrant to the right upper quadrant. The liver and gastrointestinal tract soon returned to their normal locations. Since the large cavity which remained appeared to be perfectly dry, the wound was closed in layers without drainage. During the operation the patient received 1500 cc. of whole blood.

Immediately on his return to the ward, the patient's blood pressure fell to 74/7 mm. of mercury. After administration of 0.5 gm. of caffeine-sodium benzoate and 500 cc. of whole blood, it rose to 108/80 mm. of mercury and did not drop below this level again. The patient was kept in bed for two days. During this time Wangensteen suction was applied and parenteral fluids were administered. He was then allowed to get up, with an abdominal binder for support. At this time, he was placed on a liquid diet. Aside from pain in the incision, the patient's only complaint was of bilateral shoulder pain. During the next few days, the cardiac apex and the diaphragm gradually moved down to more nearly normal positions.

By the third postoperative day the patient began taking a general diet, had a normal bowel movement, and was able to be up and about without difficulty. By the fifth postoperative day, after an additional 1000 cc. of whole blood had been given by transfusion, his hemoglobin had risen from a postoperative level of 10.1 gm. to 12.2 gm. Repeated urinalyses were within normal limits. The patient was discharged in excellent condition on the eighth postoperative day and is at present working full time at his occupation as plumber.

The specimen consisted of a huge cyst, about 30 cm. in diameter, weighing 12 kg. (26 pounds) and still containing 3 liters of fluid. The total weight of the cyst, including the 8 liters of fluid removed at operation, was thus about 21 kg. (46 pounds). The surface of the cyst was completely covered by a thick, firm, white connective tissue capsule. Its wall had an average thickness of 3 cm. It was lined with peculiar soft, gray-white, very friable villiform tissue arranged in large cotyledonous groups and supported by delicate connective tissue strands. There were discrete cystic areas, measuring 6 to 10 cm. in diameter, having separate, thick, fibrous walls and containing bloody fluid.

Microscopically, the capsule contained numerous blood vessels. Its major portion consisted of eosinophilic necrotic material showing a faint fibrous skeleton. Recent hemorrhages were seen, along with large areas of old hemolyzed blood and many brown pigment granules. Near the capsule there were frequent groups of large cells with foamy vacuolated cytoplasm and nuclei of varying shapes, usually oval or spindle shaped, bearing a close resemblance to the cells of the adrenal cortex. From the constancy with which these cells were seen in multiple sections from different areas, it was believed that they must be a constituent cell, rather than displaced remnants of adrenal cortex. It seemed reasonable to conclude that this was a cystic adenoma, most probably of adrenocortical origin, showing secondary necrosis and hemorrhage.

The fluid of the cyst was shown by culture to contain nonhemolytic *Staphylococcus albus*. Tests for bile, melanin, uroporphyrin and porphobilinogen were negative.

It is to be noted that this immense adrenal cyst had no deleterious influence on adrenal function. Evidently the opposite adrenal was fully capable of producing adequate amounts of cortical and medullary hormones, since no symptoms or signs of an endocrine nature were discovered.

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THE FAMILIAL CONGENITAL ADRENAL SYNDROME: REPORT OF TWO CASES AND REVIEW OF THE LITERATURE

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FEMALE pseudohermaphroditism is known to occur in familial association. Partially because of its apparent infrequency, as reflected by the approximately 150 reported instances, the genetic and hereditary implications are relatively unexplored. It is probable, however, that many instances of this condition are unrecognized.

Female pseudohermaphroditism is to be distinguished from true hermaphroditism. The extremely rare *true hermaphrodite* possesses gonads of both sexes, either ovotestes or a testis on one side and an ovary on the other, regardless of the extent or character of the other sexual characteristics. The *pseudohermaphrodite,* on the other hand, possesses the gonads of only one sex but, *at birth,* presents varying degrees of abnormality of wolffian and müllerian derivatives in the direction of the opposite sex. Other somatic and secondary sexual attributes also characteristically deviate toward those of the opposite sex and may develop precociously. Therefore, the classification of pseudohermaphroditism depends primarily upon the actual sex of the gonads. No matter what their location, if the gonads are testes, the individual is a *male* pseudohermaphrodite; if they are ovaries, the individual is a *female* pseudohermaphrodite.

Female pseudohermaphroditism may be developmental or endocrine in type. The developmental type is extremely rare; the endocrine type is more frequent and, as first pointed out by Marchand[1] in 1891 and by Bulloch and Sequeira[2] in 1905, is causally associated with hyperplasia of the fetal zone of the adrenal cortex occurring prenatally. Berner[3] stated that any such case in which adrenocortical hyperplasia has not been described has been insufficiently investigated. Thus, this type of female pseudohermaphroditism is probably a prenatal mani-

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festation of the adrenogenital syndrome,[4] and as such finds its analogue in the so-called sexual precocity or virilism of the male.

Apert,[5] in 1910, in a review of abnormalities of the adrenal cortex in females, recognized the association with somatosexual aberrations. He concluded that the degree of anatomic genital abnormality and the extent of alteration of the secondary sexual characteristics depend upon the period in life when the adrenal disorder becomes active. Thus, the earlier in antenatal existence the abnormal influence begins, the more extensive is the anatomic aberration of müllerian and wolffian derivatives.

It is now generally agreed that a persistent cloaca or urogenital sinus is the result of an abnormal influence which is active prior to the fifth intrauterine month before the genitalia have become fully sexually differentiated. In the female, when this influence begins later, varying degrees of masculinization of essentially female genitalia are produced. Although such an abnormal influence may have been active antenatally, it may be impossible to state with assurance whether such a process started before or after birth unless a urogenital sinus is present or genital abnormalities were observed at birth.

Two examples of the occurrence in the same family of typical female pseudohermaphroditism with a high degree of abnormality of the external genitalia, and also of somatic and secondary sexual characteristics, have come to our attention. The two girls are the only children of apparently normal, healthy parents who are not known to be consanguineous. The mother was 22 years old and the father 24 years old at the time the elder child was born. The mother has had only the two pregnancies. No known instance of a similar abnormality has occurred in the family of either the father or mother, nor is any other possible hereditary or familial abnormality known to be present. Three years and two months elapsed between the births of the first and second child. Although some doubt existed from birth as to the true sex of the first child because of genital abnormalities, nothing was done to determine definitively the nature of this defect until the birth of a second child with similar genital characteristics.

CASE REPORTS

Case 1—D. G. Y. The older child was 3 years and 5 months old when she first came under our observation. Her weight at birth was 9 pounds, 5 ounces and she was 23 inches in length. She was born after a normal, uneventful, full term pregnancy. The enlargement of the clitoris, which was noted at birth, raised some doubts as to her true sex. Subsequently, however, she was considered to be a female and was raised as a girl.

Her early development was normal in every respect (sat alone at 5 months, had her first tooth at 8 months, and walked at one year). Three "cysts," which had been noticed on the child's phallus shortly after birth, were removed when she was 9 months old. The clitoris was "trimmed," but not amputated, when she was 1½ years old. There were never any symptoms of adrenocortical insufficiency. Surprisingly, two physicians who had examined the child between the ages of 3 months and 1 year considered the external genitalia to be those of a normal female infant.

On physical examination, the general appearance was that of a distinctly feminine child (Figure 1a). The height, 37 inches, and weight, 30 pounds, were normal for her age. The only abnormalities noted were those of the external genitalia (Figure 1b). The bulging, wrinkled labioscrotal folds were strikingly prominent. There were no masses palpable or demonstrable by transillumination within the folds. Labia minora were absent. An enlarged phallus, with a well developed glans and prepuce, was present. On its ventral aspect, the phallus bore a mucosa-lined urethral groove which terminated between the labioscrotal folds at the base of the phallus in a single small orifice through which urine passed. An unbroken raphe extended from this opening to the anus. A tiny uterus was palpable. Nothing suggestive of prostatic tissue was felt. Pubic hair was absent.

A cystoscope, introduced through the orifice at the base of the phallus, revealed a urogenital sinus, approximately 3 cm. long, and what appeared to be a small vagina, 3 cm. long, terminating in an infantile cervix of normal appearance. From the anterior aspect of the urogenital sinus opposite the opening of the vagina, the cystoscope could be passed through a normal-appearing urethra, approximately 2 cm. in length, into a bladder of normal configuration. Retrograde pyelograms disclosed no

FIGURE 1 *(Case 1)*. Familial female pseudohermaphroditism. a. Patient's appearance at 41 months. b. Note prominent labia majora and protrusion of clitoris, even in erect posture.

evidence of tumor in the adrenal areas. Roentgenograms with perirenal gas insufflation were not taken.

Since the phenomena described may occur in the presence of either testes or ovaries and because the legal definition of sex depends upon the gonads, a laparotomy was performed to establish the true gonadal status. At operation a normal infantile uterus and tubes and what appeared to be ovaries were seen. Biopsy specimens of ovarian cortex and medulla were taken from both ovarian bodies. Microscopic examination of frozen sections showed normal ovarian tissue. The adrenals were not explored. A clitoridectomy was performed.

A diagnosis of female pseudohermaphroditism was established.

Case 2—D. K. Y. The second child was only 3 months old when she first came under our observation. She was delivered at full term by cesarean section. The operation was performed because the mother had an "infected tube," which was removed at the same time. At birth, the child weighed 7 pounds, 4 ounces. At first she was thought to be a girl; after three days, however, the observance of the large phallus led to doubts as to her true sex. Early weight gain, feeding habits and development were normal.

Physical examination showed a 3 month old infant, normal in every respect except for the external genitalia (Figure 2a, b). Both the internal and external genitalia were identical with those of the older sister. A laparotomy disclosed a normal uterus, tubes and what appeared to be ovaries. Biopsy specimens of ovarian cortex and medulla established the fact that the gonads consisted of true infantile ovarian tissue. A clitoridectomy was performed.

As in the case of the sister, the diagnosis of female pseudohermaphroditism was established.

Course—Subsequently, both children have been under our observation for over eight years and have developed in a manner characteristic of the type of female pseudohermaphroditism caused by antenatal adrenocortical hyperplasia.

Somatic development has been precocious in each sister. At the age of 4 years and 2 months, the older sister was somewhat tall (45¾ inches), with proportionate weight (45½ pounds), while the younger sister, then aged 23½ months, was of normal height (34 inches) and weight (23¼ pounds) for her age (Figure 3). The sparse pubic hair which each child had developed is not visible in the photograph. The large, bulging labia majora characteristic of the condition are conspicuous. The individual variability in the intensity of the postnatal masculinizing process also is now evident. The older sister appears quite feminine, while the younger child

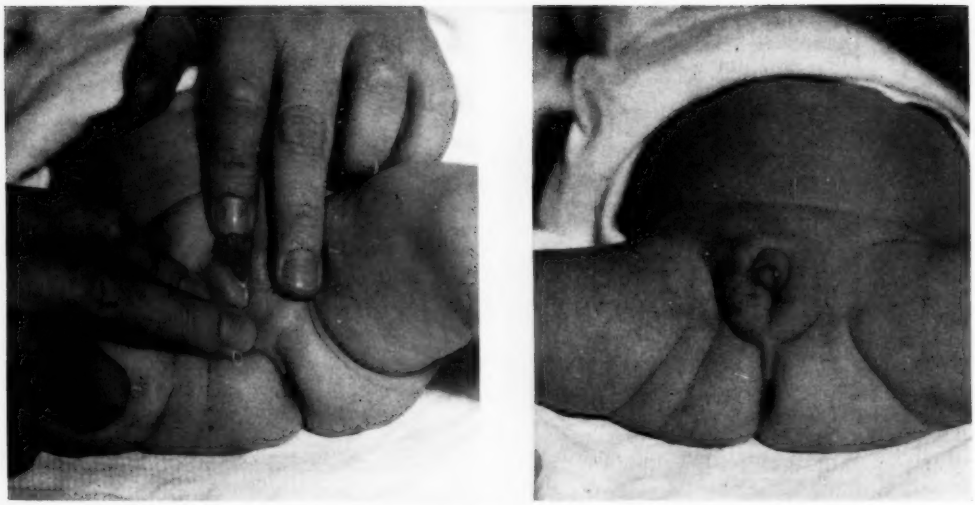


FIGURE 2 *(Case 2)*. Familial female pseudohermaphroditism. Appearance of the external genitalia at 3 months. a. Note the prominent labia majora and enlarged phallus with glans and prepuce. b. Note absent labia minora, absence of separate external vaginal opening and presence of urethral groove on phallus.

already has sturdy musculature and relatively broad shoulders. Neither sister, however, exemplifies somatic masculinization to the extent that is often found in this condition.

Separate perineal, vaginal and urethral openings were constructed surgically in each sister at the ages of 3 and 6 years, respectively. Reamputation of the clitoral stumps, which had again become hypertrophied, was performed at the same time.

When she was 7½ years old, the elder sister had slight, spontaneous vaginal bleeding which lasted for one day; a similar episode recurred two weeks later. There has been no further vaginal bleeding. Also, at this age she first developed a mild facial acne, which persists without cyclic features despite local treatment. Moderate axillary hair growth occurred and the pubic hair became profuse but remained horizontally delineated. A few dark hairs also became evident around the nipples and on the back. No mammary development was apparent.

BETWEEN the ages of 4 and 8 years, the older child grew at the rapid rate of about 3½ inches a year. At the age of 8 years and 3 months, she was somewhat tall for her age (60 inches) and weighed 96 pounds (upper normal for this height). At this time, the bone age was approximately 15 years, with little growth potential remaining. She grew only three quarters of an inch during the next six months. By the age of 10 years, she was 62 inches tall, and growth had almost ceased. There has been no further vaginal bleeding and no evidence of cyclic activity, although there was early development of the breasts. Interestingly, between the ages of 9 and 10 years she developed a craving for salt and for quantities of lemons but showed no clinical or laboratory evidence of addisonian adrenocortical insufficiency.

Between the ages of 23½ months and 6½ years, the younger sister developed a deep voice, small amounts of axillary and pubic hair appeared, and she grew rapidly. When 6½ years old, she was slightly tall for her age (52⅝ inches) and weighed 64 pounds (upper normal for this height). The bone age was far in advance of the chronologic age, but the epiphyses of all the long bones were still open and a moderate growth potential still remained. In the following six months her height increased by 1⅝ inches. Growth has continued at an undiminished rate to the age of 8 years. This sister has had no vaginal bleeding, breast development or acne. The axillary hair has become profuse and the pubic hair has extended to the umbilicus. She has had no craving for salt and no adrenocortical insufficiency has been noted.

The occurrence of this condition in siblings prompted a compilation of similar instances from the available literature in an attempt to determine whether any distinct familial patterns were apparent.

DATA COMPILED FROM THE LITERATURE

Table 1 lists the reports we have been able to uncover, in which female pseudohermaphroditism occurred in familial association with one or more other instances of somatosexual aberration.[6-45] Among 43 families, 100 instances of somatosexual abnormality have been recorded. Of these, 52 subjects were undoubtedly female pseudohermaphrodites; an additional 31 were probably female pseudohermaphrodites, although the gonadal status was not definitively determined. As this condition is analogous to the sexual precocity which presumably results from excess adrenal androgen in gonadal males, it is not surprising that 10 definite and 7 probable instances of virilism in males occurred in familial association with female pseudohermaphroditism. Of these, with the possible exception of one subject[40] in whom the somatosexual defect may have developed postnatally, a genital abnormality was either observed at birth or its congenital nature was demonstrated by developmental anomalies. Four pairs of twins with this abnormality have been recorded. Of these, two sets[33, 41] were identical twins. Whether the twins were identical was not stated in the other two reports.[7, 11]

CLINICAL SCOPE OF THE ABNORMALITY

In gonadal females, the extent of the genital abnormality at birth varied greatly. Figure 4, from Miller and Kenney,[30] portrays a sagittal section of the pelvic region of a typical female pseudohermaphrodite as exemplified by our cases. This degree of female pseudohermaphroditism, presumably the result of an abnormal influence beginning early in the embryonal period, may be easily mistaken for perineal hypospadias in a male infant. The external genitalia consist of an enlarged phallus, resembling in all respects a hypospadic penis, which originates near the apex of large, wrinkled, empty, scrotum-like labia majora. No labia minora are present, and at the base of the phallus a single opening is visible. From this opening an unbroken raphe extends dorsally to the anus. Internally, these individuals possess a urogenital sinus into which open the urethra and usually a short vagina. The cervix may be either well formed or totally absent.[22, 43, 46] The bladder may be fusiform and prostatic elements may be present. Uterus, tubes and ovaries may be fully or incompletely developed.

FIGURE 3 *(Case 1, left)*. Patient aged 4 years and 2 months. *(Case 2, right)*. Patient aged 23½ months. Compare feminine appearance of patient, Case 1, with muscular appearance of patient, Case 2.

At the other extreme—ostensibly as the result of an abnormal influence occurring late in prenatal life—is the infant in whom the only apparent abnormality at birth is an enlarged penis-like clitoris. Postnatally, if the child survives, varying degrees of somatic precocity and modification of the secondary sexual characteristics toward the male type may occur. The notable precocious developments include the early appearance of pubic, axillary and body hair and rapid, early somatic growth. The precocious tallness is a manifestation of the influence of excessive anabolic hormone, but usually occurs at the expense of the ultimate height, since the epiph-

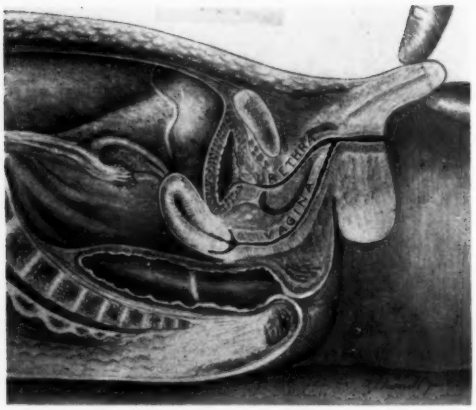


FIGURE 4. Sagittal section of pelvic region of a typical female pseudohermaphrodite. Note vaginal opening into urethra just above the perineal hypospadias. (From Miller and Kenney.[30])

yses close early.[47] To various degrees the physique becomes "masculinized."

In the most marked instances, the subjects resemble well developed males with heavy musculature, broad shoulders and narrow hips, prominent laryngeal structures, masculine hairiness with beard growth, and absence of the usual feminine contours. The voice usually becomes deep. Feminine breast development is usually lacking, but occasionally may occur without medication.[12, 25, 29]

Reports of pregnancy in "hermaphrodites" exist in the ancient literature, but are probably apocryphal. We have found no proved instance of pregnancy occurring in a female pseudohermaphrodite. Cotte[48] reported a child delivered at term by cesarean section in a female pseudohermaphrodite, but it seems doubtful that the criteria of adrenocortical hyperplasia were met.

Occasionally, bleeding from the urogenital sinus, which may be mistaken for hematuria, or irregular vaginal spotting has been noted. Physiologic menstruation is extremely rare in patients with the congenital adrenal syndrome, but apparently it may occur. Gal[16] described a 20 year old female pseudohermaphrodite of this type who "had menstruated regularly since the age of 14 years," and O'Farrell[25] stated that normal menses occurred without the aid of medication in a 24 year old female pseudohermaphrodite 25 days after an exploratory laparotomy and clitoridectomy.

In the collected cases (Table 1), there were 17 males with somatosexual abnormalities in familial association with female pseudohermaphroditism. Fifteen of these males were clinically typical examples of pseudosexual precocity, while two,[20, 24] as pointed out by Werthemann[24] and Seckel,[49] presented an admixture of precociously and incompletely developed external genitalia. In this context, Neugebauer[11] noted that bilateral adrenal hyperplasia was present in 0.7 per cent of male pseudohermaphrodites. Development of the genital primordia in the female direction in individuals both gonadally and otherwise somatically male has also been associated with adrenocortical abnormality.[50-52] It seems paradoxical that incomplete masculinization of gonadal males has occurred[21, 24] in the same families in which gonadal females have been masculinized.

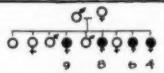
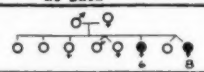
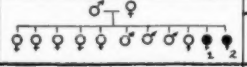
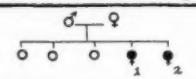
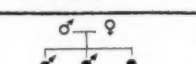
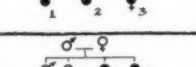
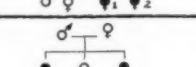
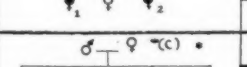
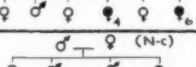
ETIOLOGY

The fundamental etiology of pseudohermaphroditism, as well as the exact mechanisms of sex differentiation, are unknown. The most reasonable supposition at the present time is that genetic factors initiate the chain of processes causing sexual differentiation in the male or female direction,[53] and that most, if not all, female pseudohermaphrodites possess the female XX chromosomal constitution.

GENETIC IMPLICATIONS

In none of the families included in this study was a somatosexual abnormality known to have occurred in more than a single generation. When a rare developmental abnormality occurs in a single generation only, the influence of a rare recessive gene may be suspected.[54] Evidence for this hypothesis depends upon a high incidence of consanguinity, as in the case of gargoylism.[55] The total number of reported cases of familial congenital adrenocortical hyperplasia is so small that such evidence cannot be evaluated. Against the hypothesis in this syndrome is the explosive occurrence of multiple instances of the congenital adrenogenital syndrome among the children of brothers and sisters of nonconsanguineous parents.[25] This fact would also indicate that the characteristic is not sex-linked.

TABLE 1. CASES OF THE FAMILIAL CONGENITAL ADRENAL SYNDROME.

REFERENCE	FAMILY CONSTELLATION	SIB	AGE	GONADS	EXTERNAL GENITALIA	INTERNAL SEX ORGANS	ADRENALS	ADRENOCORTICAL INSUFF.	REMARKS
Curling 1862	No Data	1	7 wks.	F	Hypospadic phallus; bifid scrotal folds.	Uro-genital sinus; ovaries; uterus.			Twins. Died age 7 wks. and 9 wks. respectively.
		2	9 wks.	F	Same as (1).	Same as (1).			
Ogston 1872	No Data	1	5 yrs.	F	Clitoris enlarged; pubic hair	Uterus; ovaries	75 gms. tot.		Both died of 'cholera-like' diarrhea on same day.
		2	12 yrs.	F	Same as (1).	Same as (1).	90 gms. tot.		
Griffith 1877	No Data	1	"child."	F	Hypospadic phallus.	Uterus; ovaries			Both children died of unstated cause.
		2	"child."	F	"Male".	"Female".			
Phillips 1886	 **	4	19 days	F	Large clitoris and labia majora, absent labia minora.	Uro-genital sinus; "entirely female".	"very large"	"gradually wasted and died"	
		6	40 days	F	Same as (1).	Same as (4)		Same as (4).	
		8	59 days	F	Same as (1).	Same as (4)		Same as (4).	
		9	24 days	F	Same as (1).	Same as (4)		Same as (4).	
Hadosy 1907	No Data	1	15 minutes	F	"Female External Hermaphrodites".	"Ovaries and uterus in each pelvis".			Double monsters joined at head and thorax.
		2		F					
Durlacher 1912		6	21 mos.	F	Enlarged hypospadic phallus; vagina.				Breast development; pubic hair.
		8	3 mos.	F	"Phallus size of that of a 15 yr. - old boy; other female organs normal.				
Mathias 1922 Schmidt 1924		1	42 yrs.	F	Clitoris enlarged.	Ovaries; uterus.	44 gms. ea.		Case of F. Fraenkel
		2	23 yrs.	F	Clitoris enlarged; shallow vestibule; no external vagina.	Myomatous uterus; ovaries; thin, hypoplastic vagina.			Case of Kustner. No menses; shaved aet. 14 yrs., alopecia aet. 20 yrs.
Loser, Israel 1923		1	21 yrs.	F	Clitoris enlarged; vagina 4 cm. deep.	Uterus; ovaries.	Pneumorcent.: Left large.		Shaved daily.
		2	19 yrs.	F	Same as (1).	Same as (1).	Same as (1).		Shaved daily.
Gal 1924	No Data	1	20 yrs.	F	Hypospadic phallus; no external vagina; absent labia minora.	Palpable uterus and ovaries.			"Regular menses since aet. 14 yrs."
		2	21 yrs.	F	Same as (1).	Same as (1).			No menses.
Scabell 1924		1			"Premature; male sex".			Malnutrition & cachexia	Died.
		2	3 mos.		"Brother".		19 gms. tot.	emesis; emaciated; died.	Pyloric Stenosis suspected clinically.
		3	4 mos.	F	Enlarged hypospadic phallus.	Uterus; ovaries; uro-genital sinus; rudimentary prostate.	enlarged.	emesis; emaciated; died.	
Weresohinski 1924		1	29 yrs.	F	Enlarged clitoris; no external vagina; absent labia minora.	Rudimentary vagina & uterus; tiny ovaries.			"Malignant hypernephroma"; Ovarian follicles, corpus lut.
		2	"older"	F	"More abnormal than sister".				
Fruchaud, Vialle 1926		1	17 yrs.	F	Large clitoris and labia majora; absent labia minora; palpable prostate.	Uro-genital sinus; ovaries.			Graafian follicles.
		2	24 yrs.	F	Same as (1) except no prostate palpable.	Ovaries; rudimentary uterus			Ovarian follicles and corpora lutea.
Orel 1929 Priesel 1931	 *	3	28 mos.	M	Large penis; cryptorchid; pubic hair.		Hypertrophied	Brown cutaneous pigmentation.	Died with convulsions.
		4	5½ yrs.	F	Hypospadic phallus; large labia majora; pubic hair.	Uro-genital sinus; uterus; ovaries; prostatic ducts.	Hyperplastic	Brown cutaneous pigmentation.	Died. Bone age 18 yrs. (X-ray).
Rupilius 1933	(N-C)	4	4 mos.	F	"Male with hypospadias"; bifid scrotum without testes.	"Entirely female; small ovaries".		Died of "intestinal disturbances".	Born one month prematurely.
		6	1 mo.	F	Hypospadic phallus; large labia majora; no external vagina.	Blind vagina; uterus; ovaries.	Enlarged	Died of "severe vomiting and diarrhea".	Full term delivery.
Bayer, Lang 1934	 (N-c)	2	still-born	F	Large clitoris; vagina	Uterus; ovaries.	Hyperplastic		
		4	8½ yrs.	M	"Precociously developed male".				

* (C) = Consanguineous; (N-C) = Non-consanguineous.

** ○ Normal child: ♂ Male; ♀ Female.
● Female child with the congenital adrenal syndrome (female pseudohermaphrodite).
● Male child with the congenital adrenal syndrome.

TABLE I (CONTINUED)

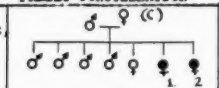
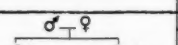
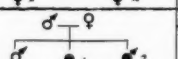
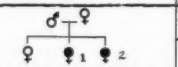
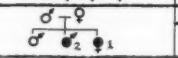
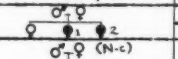
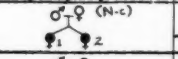
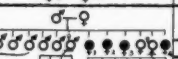
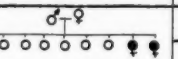
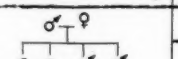
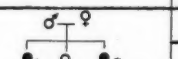
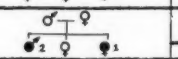
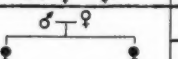
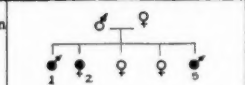
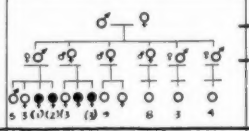
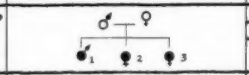
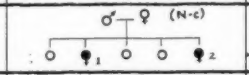
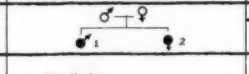
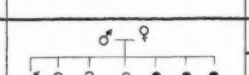
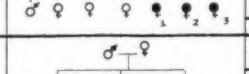
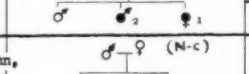
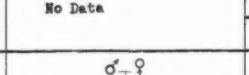
REFERENCE	FAMILY CONSTELLATION	SIB	AGE	GONADS	EXTERNAL GENITALIA	INTERNAL SEX ORGANS	ADRENALS	ADRENOCORTICAL INSUFF.	REMARKS
Pla, Sanchez, Granotich 1944		1	18 yrs.	F	Enlarged hypospadic phallus, large labia majora, rudimentary labia minora, tiny vagina, rudimentary cervix.	(Utero-salpingography) Prepuberal uterus; patent tubes.			Muscular; deep voice; shaves every other day.
		2	14 yrs.	F	Same as (1).	Same as (1).			Same as (1).
McIntosh, Brown 1945		1	6 yrs.	F	Enlarged clitoris.	"Infantile uterus; ovaries"	Hyperplastic		Sex doubted from birth; died.
		2	5 yrs.	F	Hypospadic phallus, vaginal opening "partially obscured".	Rudimentary uterus; ovaries.	Same as (1).		X-ray irradiation of adrenals without effect.
Thelander 1941 1946		1	5 wks.	F	"Hypospadias".			Clinically diagnosed.	Died aet. 5 wks.
		2	6 yrs.	M	Large penis; pubic hair at 14 mos.	"Male"	74 gms. tot.	Clinical and Laboratory diagnosis.	DCA-treated from infancy to death aet. 6 yrs.; increased basophils in ant. pituitary.
Biggs, Rose 1947		1	6 wks.	F	Enlarged hypospadic phallus.	Uro-genital sinus; uterus; ovaries.	16 gms. tot.	Persistent emesis; weight loss; death.	Increased basophils in anterior pituitary.
		2	4 wks.	F	Same as (1).	Same as (1).	Same as (1).	Sudden vomiting; death within 24 hours.	No clitoral hypertrophy at birth.
Apert 1926 (from Biggs & Rose,'47)	No Data	1	?	F	"Clitoral hypertrophy"				Unable to verify original reference.
		2	?	F	"Clitoral hypertrophy"				
Hain 1947		1	2½ yrs.	F	"Enlarged phallus at birth".				17-ketosteroids elevated.
		2	17 yrs.	F					"Had the same abnormality" as (1).
		3	19 yrs.	F					
Hain 1947		1	2½ yrs.	F	Enlarged phallus; pubic hair.	Uterus; ovaries.			17-ketosteroids elevated.
		2	11 yrs.	M	Large penis; testes; pubic hair.				"Tumor over left kidney"; 17-ketosteroids elevated.
Hain 1947		1	21 yrs.	F	Enlarged phallus	Uterus; ovaries.	Enlarged		17-ketosteroids elevated.
		2	16 yrs.	F	Same as (1).				Same as (1).
Collier 1948		1	52 days	F	Enlarged phallus; tiny vagina and cervix.				Identical twins with one placenta and two cords.
		2	52 days	F	Same as (1).				
Deming, Goetsch, Kuna 1949		1	23 yrs.	F	Enlarged phallus; short vagina; normal cervix.	Small uterus; ovaries.	"Not palpable".		Urinary gonadotrophins 13 m.u. Masculine appearance; hirsute.
		2	42 yrs.	F	Enlarged clitoris at birth.	Same as (1).	Same as (1)		Stilbestrol 50 mgm. daily.
		3		F	"Female pseudohermaphrodite".				Both died in infancy "of infectious disease".
		4		F	"Female pseudohermaphrodite".				
Zuelzer, Blum 1949		1	6 wks.	F	"Penis, but no scrotum; thought to be a boy".			Died aet. 6 wks. of "diarrhea and malnutrition".	
		2	20 wks.	F	Hypospadic phallus; absent labia minora.	Uro-genital sinus; uterus; ovaries.	17 gms. tot. adenomas	Clinical and laboratory diagnosis.	Died aet. 20 wks. Increased basophils in ant. pituitary.
Lewis, Wilkins 1949		1	6½ yrs.	F	Pubic hair at 5 yrs.	Uro-genital sinus; uterus; ovaries.	"Normal at laparotomy"		
		3		M	"Precocious sexual development with small testes".		Hyperplastic		
		4		M	"Precocious sexual development with small testes".		Hyperplastic		
Deamer 1950		1	4 mos.	F	Enlarged hypospadic phallus.	Uro-genital sinus; uterus; ovaries.	Hyperplastic	Clinical and laboratory diagnosis.	Died aet. 4 mos. Mature ovarian follicles.
		2	6 wks.	F	Same as (1).	Uro-genital sinus.		Clinical and laboratory diagnosis.	Well-controlled on DCA therapy. Being raised as a boy.
Deamer 1950		1	3 wks.	F	Enlarged hypospadic phallus; large labia majora; absent labia minora.	Uro-genital sinus; uterus (to X-ray); prostate.		Clinical and laboratory diagnosis.	17-ketosteroids elevated.
		2	3 mos.	M	"Male".			Emesis; weight loss.	Died aet. 3 mos.
Bentinok, Lisser, Traut, Hinman 1951		1	3½ yrs.	F	Enlarged hypospadic phallus; large labia majora; absent labia minora.	Uro-genital sinus; uterus; ovaries.			17-ketosteroids elevated.
		2	3 mos.	F	Same as (1).	Same as (1).			Same as (1).

TABLE I (CONTINUED)

REFERENCE	FAMILY CONSTELLATION	SIB	AGE	GONADS	EXTERNAL GENITALIA	INTERNAL SEX ORGANS	ADRENALS	ADRENOCORTICAL INSUFF.	REMARKS
Werthemann 1935		1	8 wks.	M	Hypospadic phallus; bifid scrotum; cryptorchid.	Vas deferens; seminal vesicles; prostate.	23 gms. tot.	Skin pigmentation; persistent emesis; death.	
		2	12 wks.	F	Enlarged clitoris; no external vagina.	Uterus; ovaries.	24 gms. tot.	Apathy; vomiting; weight loss; death.	
		5	8 wks.	M	Hypospadic phallus; bifid scrotum; testes descended into scrotum.	Same as (1).	Same as (1).	Same as (1).	
O'Farrell 1935		(1)	19 yrs.	F	Adult-sized, hypospadic phallus.	Uterus; right ovary "cystic"; left ovary absent.			Masculine appearance; beard.
		(2)	24 yrs.	F	Adult-sized, hypospadic phallus.	Uterus; ovaries.			"Normal menses 25 days after clitoridectomy alone".
		(3)	9 yrs.	F	Hypospadic phallus; no external vagina.	Uterus; ovaries.	Enlarged (Wilkins,'40)		Feminine appearance; well-developed breasts. Two other children stated to be female pseudohermaphrodites.
Jacobsimer, Gorfinkel 1936		1	5 yrs.	M	Adult penis, testes and prostate.				Bone age (X-ray) 8-9 yrs.
		2	3 yrs.	F	Enlarged clitoris; normal vagina.				Bone age (X-ray) 7-8 yrs.
		3	7 mos.	F	Enlarged clitoris; no external vagina at birth.				Fine pubic hair.
Polzer, Priesel 1937		1	5 mos.	F	Enlarged clitoris; no external vagina.	Uro-genital sinus; uterus; ovaries; prostate.	Enlarged	Frequent infections; weight loss; emaciation; terminal pneumonia.	
		2	2mos.	F	Same as (1).	Same as (1).	Same as (1).	Same as (1).	
Carlisle, Geiger 1938		1	9 yrs.	M	Precociously developed male.				Pubic and axillary hair.
		2	3 yrs.	F	Enlarged clitoris; no external vagina; absent labia minora.	Uro-genital sinus; uterus; ovaries.			Many Graafian follicles in ovary by biopsy.
Young 1937	No Data	1	16 yrs.	F	Enlarged clitoris; no external vagina.	Uro-genital sinus; uterus; ovaries.	Enlarged		
		2	12 yrs.	F	Same as (1).	Same as (1).	Same as (1).		
Young 1937	No Data	1	16 yrs.	F	Enlarged hypospadic phallus, no external vagina.	"Infantile uterus; ovaries"	Enlarged (X-ray)		Masculine appearance; beard; male social role.
		2	6 yrs.	F	Same as (1).				Female social role; same as (1).
Young 1937	No Data	1	3 yrs.	F	Hypospadic phallus; pubic hair.	Uro-genital sinus; uterus; ovaries.	? Enlarged		
		2	8 mos.	M	"Baby brother; hypospadic phallus; bifid scrotum; cryptorchid."				
Smith, Stockwell 1940		1	13 yrs.	F	Enlarged phallus; absent hymen.	Uro-genital sinus; uterus; ovaries.			Developed masculine appearance, deep voice, pubic hair at 7 yrs.
		2	9 yrs.	F	"Well-developed penis; rudimentary labia and cervix".	Same as (1).			"Feminine figure with hips, breasts and pubic hair."
		3	3 yrs.	F	Same as (1); rudimentary cervix.	Uro-genital sinus.			
Miller, Kenney 1940		1	10 yrs.	F	Enlarged, hypospadic phallus; bifid scrotum.	Uro-genital sinus; uterus; ovaries.	Left 40 gms.; right absent.	Skin darkly pigmented.	Died of post-operative retroperitoneal hemorrhage.
		2	still-born	M	"Brother with hypospadias".				Female pseudohermaphrodite?
Wilkins, Fleischmann, Howard 1940		1	4 yrs.	M	"Adult penis, scrotum and testes; prostate large for age".		27 gms. tot.	Feeding problem; salt craving; emesis; serum Na = 111 mEq/l; died.	Similar tissue in testes and adrenals; increased basophils in anterior pituitary.
		2			"Characteristic abnormalities of a female pseudohermaphrodite".				Died aet. 5 weeks.
Bratrud, Thompson 1943	No Data	1	15 days	M	"Male".	"Male; large prostate".	19 gms. tot.	Anoroxia; weight loss; emesis; dehydration.	Died aet. 15 days.
		2	42 days	F	Enlarged hypospadic phallus	Uro-genital sinus; uterus; ovaries; small prostate.	20 gms. tot.	Same as (1).	Recurrent pyelitis; died aet. 42 days.
Rhodes 1943		1	7 wks.	F	"hypospadic phallus; bifid scrotum without palpable masses".				Identical twins with one placenta and two cords. Rectal examination "inconclusive" as to pelvic organs.
		2	7 wks.	F	Same as (1).				

Stern[56] stated that dominant genes with low penetrance may be responsible for hermaphroditism. Possibly the characteristic begins as a mutant gene which is transmitted as a dominant with low penetrance through both sexes. The characteristic may have "anticipatory" properties, becoming either progressively "stronger" or penetrant or occurring progressively earlier in life with each succeeding generation in which it is present. The mutant allele may then disappear from the genic populations when the affected individual dies without offspring. In this way, it is conceivable that a mutant characteristic might occur in either parent of one generation, be transmitted without known manifestation through some of their male and female offspring to appear clinically in the third generation. By the fourth generation of its presence, the trait, by "anticipatory" behavior, might have become "lethal," any affected zygotes being aborted early in intrauterine life. In this respect, detailed family histories regarding the incidence of abortions and miscarriages would be of possible interest.

Alternatively, the trait may be a fairly prevalent genetic characteristic transmitted through both sexes. By "anticipatory" behavior, or by changes in penetrance, this characteristic might rarely be manifested as a clinical somatosexual defect or, if more extreme, act lethally upon the zygote.

Examples of somewhat similar "anticipatory" behavior may be represented by such conditions as diabetes mellitus or Huntington's chorea, which are known to have familial aspects and which may tend to become clinically apparent at progressively younger ages with each succeeding generation. As pointed out by Stern,[56] however, "anticipation" may be only a statistical figment, or such observations may be based upon other than genetic factors.

SEX RATIO

Disturbances in the sex ratio at birth, as well as the differential sex incidence of affected individuals, in a sense, may be a manifestation of "anticipatory" behavior. The various manifestations of the adrenogenital syndrome reportedly occur with greater frequency in females than in males.[57,58] It is possible that this sex incidence is more apparent than real, since the deviation from normal is more striking in females. Nevertheless, it is impressive that in those sibships in which female pseudohermaphroditism occurs and in which a complete accounting of all siblings is recorded, approximately two gonadal females are born to one gonadal male (Table 2)—a conspicuous disturbance in the sex ratio.

Normally, more boys are born than girls, the sex ratio at birth remaining relatively stable at about 1040 males to 1000 females;[59] however, the greater viability of the female is well recognized. Crew[60,61] pointed out the selective elimination of males both before and after birth. Parkes[62-64] concluded that the sex ratio at conception is at least 120 males to 100 females and called attention to the preponderance of male embryos in spontaneous abortions.

This differential viability suggests a greater susceptibility of the male zygote to lethal influences. The possibility that congenital adrenal hyperplasia may play a role in the selective elimination of a larger number of male than female embryos might account in part for the preponderance of female births. Confirmatory of this, and suggesting that the adrenocortical abnormality may be more far reaching and of more serious consequence in males, is the fivefold greater incidence of postnatal adrenocortical insufficiency in males than in females.[58]

THE ADRENAL CORTEX IN THE CONGENITAL ADRENAL SYNDROME

In all of the 32 cases (Table 1) in which definitive examination was made either at operation or at autopsy, the adrenals were grossly enlarged. Roentgenograms of the adrenal areas following perirenal insufflation in 3 patients demonstrated adrenal enlargement in all. The enlargement was bilateral in all but 1 patient,[30] in whom the right adrenal was absent. In those cases where microscopic examination was performed, adrenocortical hyperplasia was found. Adrenocortical adenomas[65] and carcinomas[18,66,67] also have been reported in the congenital adrenogenital syndrome. One case of sarcomatous degeneration of hyperplastic adrenocortical tissue in a 70 year old female pseudohermaphrodite has been reported.[68]

The hyperplasia, which is believed to originate in the juxtamedullary or reticular zone, produces varying degrees of distortion of the adrenocortical architecture. In the case reported by Wilkins,[31] no evidence of fascicular or glomerular zones was found. In males with this

syndrome similar hyperplastic tissue also has been found in the testes.[31, 36, 50, 69, 70]

URINARY EXCRETION OF 17-KETOSTEROIDS AND PREGNANEDIOL

The excretion of urinary 17-ketosteroids was determined in 10 subjects in this series and was found to be elevated in all (Table 1). The excretion of pregnanediol is variable in the congenital adrenogenital syndrome. Hain[71] stated that female and male pseudohermaphroditism may be differentiated on the basis of the excretion of urinary 17-ketosteroids; if the 17-ketosteroid content is increased, the individual is a female pseudohermaphrodite; if normal or only slightly elevated, a male pseudohermaphrodite. This differential point, however, is not always valid since the excretion of 17-ketosteroids may be normal, the factor of age being considered,[72-77] or only slightly elevated in female pseudohermaphroditism. Also, as noted by Neu-

TABLE 2

INCIDENCE OF MALE AND FEMALE BIRTHS AND SEX RATIO IN THE SIBSHIPS OF THE FAMILIAL CONGENITAL ADRENAL SYNDROME

REFERENCE	TOTAL CHILDREN IN SIBSHIP			
	Male children		*Female children*	
	Normal	With Congenital Adrenal Syndrome	With Congenital Adrenal Syndrome	Normal
Phillips[10] 1886	2	0	4	2
Fraenkel, reported by Mathias[18] 1922 and by Schmidt[14]	3	0	2	6
Wereschinski[19] 1924	1	0	2	1
Fruchaud, et al.[19] 1926	0	0	2	1
Rupilius[22] 1933	1	0	2	3
O'Farrell[25] 1935	5	0	1	3
O'Farrell[25] 1935	0	0	2	3
Werthemann[24] 1935	0	2	1	2
Jacobzimer, et al.[26] 1936	0	1	2	0
Smith, et al.[29] 1940	1	0	3	3
Wilkins, et al.[31] 1940	0	1	1	0
Pla, et al.[34] 1944	4	0	2	1
McIntosh, et al.[35] 1945	0	0	2	0
Biggs, et al.[38] 1947	0	0	2	1
Hain[40] 1947	2	0	3	0
Hain[40] 1947	1	1	1	0
Hain[40] 1947	0	0	2	1
Collier[41] 1948	0	0	2	0
Deming, et al.[42] 1949	8	0	4	2
Lewis, et al.[44] 1949	0	2	1	1
Deamer[45] 1950	0	1	1	1
Deamer[45] 1950	0	0	2	1
Bentinck, et al. 1952	0	0	2	0
TOTAL	28	8	46	32

TOTAL MALES: 36

TOTAL FEMALES: 78

Sex Ratio: 2.17 Females — 1.00 Male

gebauer[11] and clinically demonstrated in several instances,[16,24,50,52,69] genital abnormalities indistinguishable from those of female pseudohermaphroditism may occur in gonadal males in association with adrenocortical hyperplasia.

There does not appear to be any consistent relationship between the level of the urinary 17-ketosteroid excretion and the degree of genital abnormality or the subsequent intensity and extent of the virilizing process.

ASSOCIATED ADDISONIAN ADRENOCORTICAL INSUFFICIENCY

Early death frequently is associated with the congenital adrenal syndrome. In the 100 cases listed in Table 1, 43 patients died in childhood; of these, 33 died before the age of 6 months. A history of failure to gain weight, feeding problems, unexplained episodes of vomiting or diarrhea, craving for salty foods and susceptibility to infections was often present in those who died. Such individuals, following a period of feeding difficulties and failure to gain weight, usually developed intractable vomiting and became dehydrated before death. Brownish pigmentation of the skin was occasionally noted. On this basis some of the earlier observers suspected addisonian adrenocortical insufficiency. This suspicion has subsequently been verified in several instances of the congenital adrenal syndrome in which a similar clinical picture, in addition to the chemical laboratory findings typical of Addison's disease, has been demonstrated.[31,32,36,37,43,45,76,78]

Addisonian adrenocortical insufficiency was either suggested or proved in 29 of the patients recorded in Table 1. Of these 29 subjects, 9 were gonadal males and 20 gonadal females. Of the entire series of patients with the congenital adrenal syndrome listed in Table 1, 56 per cent of the males, but only 24 per cent of the females, showed evidence of this form of adrenocortical insufficiency. Adrenocortical insufficiency may be apparent shortly after birth or may not become manifest until after the first year of life.

Lewis and Wilkins[79] have suggested that in the congenital adrenal syndrome associated with addisonian crises, the adrenal glands secrete steroids which promote sodium excretion rather than sodium retention. In accord with this, Mason and Kepler[80] have isolated an abnormal 11-oxysteroid from patients with congenital adrenocortical hyperplasia, and ACTH has been reported to evoke a qualitatively different secretory response from the adrenal cortex in such individuals.[79,81]

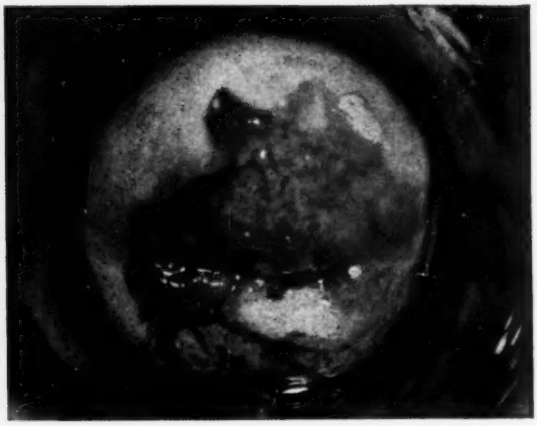
The frequency with which the familial congenital adrenal syndrome and addisonian adrenocortical insufficiency are associated suggests that adrenocortical insufficiency should be suspected in any child in whom unexplained vomiting or diarrhea, feeding problems, failure to gain weight, susceptibility to infections, craving for salt or salty foods, and brownish mucosal and cutaneous pigmentation, or any of these alone, is combined with a family history of a somatosexual abnormality. Conversely, in a sibship which includes one or more examples of the congenital adrenal syndrome, the history that another sibling died of "pyloric stenosis,"[82] "projectile vomiting," or "starvation" suggests that it also may have had the congenital adrenal syndrome with adrenocortical insufficiency. Therefore, addisonian adrenocortical insufficiency is a primary diagnostic and therapeutic consideration in pseudohermaphrodites and their siblings.

References cited in this article will be included in the authors' reprints.

THE OFFICE CLINIC

MEDICAL LITERATURE abounds with descriptions of new diagnostic equipment, most of which is highly specialized and quite expensive. However, most cases of cancer can be diagnosed, at least tentatively, by the use of instruments found in nearly every physician's office. The proper and frequent use of speculums, laryngeal mirrors, proctoscopes, tongue depressors, stethoscopes, biopsy forceps and the like are necessary for the salvation of many cancer patients. But the most important and most useable tools owned by a physician are his five senses, his suspicions, and his logic. On the next three pages are pictures and accompanying facts which test the efficiency of these tools. Here are six patients as they would appear in any physician's office. Each presents a particular problem of diagnosis or treatment. The reader is invited to compare the way in which he would solve that problem with the way in which it was actually solved. For it is in the solution of just such problems that every doctor's office will become a cancer detection center.

(Reproduced from THE CANCER BULLETIN)



THIS woman complained of a heavy vaginal discharge and bleeding of one year's duration. On admission, this cervical condition was revealed. What is the probable diagnosis and treatment?

CARCINOMA of the cervix, League of Nations Stage I. Lesions in this stage are confined to the cervix, and respond well to radium treatment.

THE left breast of this patient has always been the larger. In October, 1949, this breast was injured by a cotton bale; in July, 1950, biopsy revealed cancer. Should trauma be suspected as the cause?

PROBABLY not. The patient always had a larger left breast (unilateral gynecomastia), which could well have predisposed this breast to carcinoma. Any deviation from normal in the male breast demands investigation and explanation.

On admission, the patient presented this small penile lesion. He denied having or ever having had syphilis or other venereal disease. What diagnostic procedures are indicated in this case?

A Wassermann should be carried out; if negative, a biopsy of the lesion is indicated. In this case, the lesion suggested the presence of syphilis, but the Wassermann was negative. Carcinoma of the penis was found on microscopic examination.

This five-year-old lesion, which the patient often burns with a cigarette, has shown accelerated growth in recent months. Medical treatment has failed. What procedures are now indicated?

Although the lesion appeared to be leukoplakic, biopsy was indicated in this patient, and showed an early squamous cell carcinoma. Results of treatment were excellent. Had the patient's lesion not been biopsied, or had he received inadequate treatment over a period of even a few months, the patient could very easily have lost his life.

Less than one month before this picture was made, the patient squeezed a blackhead on his nose. A small sore soon developed and he consulted his physician at once. Should cancer be suspected?

Yes. Any sore which does not heal within two weeks demands biopsy. In this case, a biopsy revealed squamous cell carcinoma. Because of early diagnosis, this patient could be treated with x-ray therapy. Treatment caused regression of the lesion, and cosmetic results were excellent.

This patient has a history of thyroid cancer which was treated by surgery and x-radiation. Present roentgenograms suggest widespread metastases. What palliative therapy may be used?

Further surgery would have been of little value. Therefore, this patient was given radioiodine, which caused some regression of the tumor, and afforded palliation for the patient until her death.

MORTALITY IN SURGICALLY TREATED ADRENOCORTICAL TUMORS

I. Report of Three Cases of Cushing's Syndrome Due to Adrenocortical Tumors

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SINCE Cushing's classical description in 1932 of the disease which now bears his name,[1] much has been added to basic concepts of the condition, notably its frequent association with hyperplasia or tumor of the adrenal cortex. The high mortality incident to the surgical treatment of the latter has been the source of great concern. The problem is exemplified in the ensuing report which deals with three instances of Cushing's syndrome where the responsible adrenocortical tumor was dealt with surgically.

GOLDBERG

DEAMER

Case 1—Mrs. E. Z., aged 39 years, had been labelled a psychoneurotic because of the bizarre pattern and multiplicity of her complaints over a period of four years. Her chief disability was increasing weakness, especially of the lower extremities, noted particularly when climbing stairs or boarding streetcars. Additional symptoms included amenorrhea, advancing hirsutism, increasing nervousness and palpitation, and frequency and urgency of urination. She bruised easily and also had transient episodes of edema of the ankles. She volunteered that she had a "ferocious appetite" which necessitated a constant and determined effort at caloric restriction in order to avoid accumulation of excessive weight. An attack of rubella in March 1949, six months previously, had so sapped her flagging vitality that she felt as if her "strength and substance were ebbing day by day."

Previous medical treatment, which included administration of desiccated thyroid substance, potassium iodide, stilbestrol and nicotinic acid, had not benefited the patient, but subjective improvement was claimed from a proprietary mixture of amino acids and vitamin B complex, which the patient took upon her own initiative.

Physical examination showed a somewhat short and plump woman with conspicuously slender forearms and legs (Figure 1). The face

From the Endocrine Clinic of the Division of Medicine and the Divisions of Pediatrics and Surgery (Urology), University of California School of Medicine, San Francisco, California.

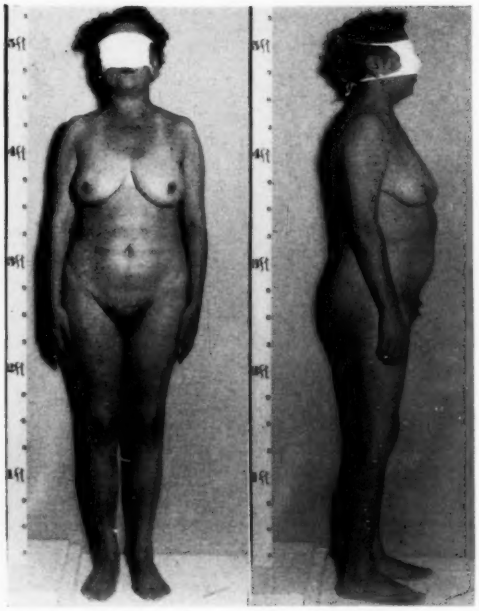

FIGURE 1a and b. Note disproportion between spindly arms and legs and the trunk, despite the absence of obesity. Fine hirsutism fails to show in photograph.

was inclined to be round and full, somewhat dusky and scarred from acne. Hirsutism was not apparent because of epilation. The eyes were prominent and the lids edematous and reddened. The skin was thin, dry and atrophic, and showed numerous ecchymoses but no purplish striae. Soft, fine hair covered the sacrum and thighs. The eyes, including pupils, extraocular muscles, fundi and fields, were normal. The teeth were in excellent condition. The thyroid was small and without nodules. The breasts were pendulous but otherwise not remarkable. The rib cage was tender, especially over the left side posteriorly. The lungs were clear. The heart was enlarged to the left; there were no murmurs. The pulse rate was 72 per minute with numerous ventricular extrasystoles; the blood pressure was 180/120. The abdominal musculature was flabby and the liver was just palpable below the costal margin. The hands were remarkable only for exceptionally strong fingernails. The reflexes were normal. The clitoris, cervix and uterus were normal. There were no adnexal masses.

Results of laboratory tests are recorded in

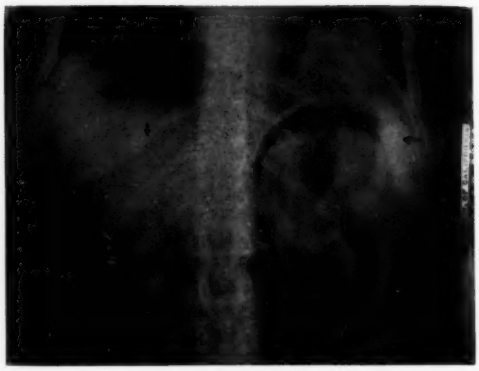

FIGURE 2. Perirenal insufflation (600 cc. carbon monoxide) showing large spherical tumor above the left kidney. Also note the callus formation at the site of the fractured ribs.

Table 1, column 1. Attention should be directed to the hemoconcentration, the leukocytosis, lymphopenia and eosinopenia, the diabetic glucose tolerance test, and the very high content of 17-ketosteroids and 11-oxysteroids in the urine. An electrocardiogram was of the type associated with left ventricular hypertrophy and recorded occasional ventricular ectopic beats. Roentgenograms of the spine, skull and ribs showed moderate and uniform osteoporosis. There were partially healed fractures of the sixth, eighth and tenth ribs on the right side and of the eighth rib on the left. The skull showed no abnormalities other than the osteoporosis. Intravenous urograms on two occasions failed to show evidence of an adrenal tumor, but after the injection of 600 cc. of carbon monoxide gas into the left perirenal space, roentgenograms clearly revealed a large spherical tumor above the left kidney (Figure 2).

With the diagnosis and localization of the tumor complete, there seemed no alternative but surgical removal of the tumor, despite recognition of the hazards involved. (Preoperative therapy is detailed in Table 2.)

OPERATION

The tumor, exposed through a supradiaphragmatic approach, was firm, spherical and well encapsulated. The mass, which measured 9 cm. in diameter, and the pedicle, measuring 1.5 cm. in length, which formed its at-

tachment, were removed together with about seven-eighths of the left adrenal. The pleura was inadvertently opened, but repair was made promptly. The patient was returned to the ward in good condition, with a pulse rate of 85 and a blood pressure of 140/80. By the next day the pulse rate and respiration had quickened, the temperature had risen, and the patient showed respiratory embarrassment. Removal of 450 cc. of bloody fluid from the left side of the chest brought some relief. Treatment as summarized in Table 2 was instituted, but the respiratory embarrassment grew progressively worse and the urinary output decreased. The patient final-

TABLE 1

LABORATORY DATA, CASE 1

	OUTSIDE LABORATORY 9-27-48	PREOPERATIVE (U.C.H.) 10-48	POSTOPERATIVE 11-4-48	POSTOPERATIVE 11-6-48
Blood count				
Hemoglobin	100% 14.5 gm.	14.0 gm.		
RBC	5,100,000	5,400,000		
WBC	13,600	9,450		
PMN	85%	56%		
Lymph.	14%	41%		
Mono.	1%	2%		
Hematocrit	46%	47%	46%	
Sed. rate	5 mm./hr.			
Eosinophil count	44/cu. mm. (normal 100-300)			
Wassermann test	Negative			
Urine				
Sp. gravity	1.020	1.013		
Reaction	Acid	6.0		
Albumin	+	+		
Glucose	0	+		
Microscopic	Negative	Loaded with WBC		
Blood chemistry				
Oral glucose tolerance Test (100 gm. glucose)	*Blood* *Urine*			
Fasting	105 mg. % Negative			
½ hr.	160 mg. % +			
1 hr.	250 mg. % +++			
2 hrs.	278 mg. % +++			
3 hrs.	200 mg. % +++			
Blood serum Ca.	10.5 mg. %			
Blood serum P.	2.2 mg. %			
Alk. phosphatase	1 Bodansky unit			
Total protein	6.4 gm. %			
Total albumin	4.9 gm. %			
Total globulin	1.5 gm. %			
Nonprotein nitrogen	42.3 mg. %	27 mg. %	27 mg. %	
Urea		17 mg. %		
Creatinine		1.5 mg. %		
Uric acid		1.4 mg. %		
Blood serum Na.	119 mEq./L	137 mEq./L	138 mEq./L	138 mEq./L
Blood serum K	5.8 mEq./L	3.9 mEq./L	3.0 mEq./L	3.0 mEq./L
Blood serum CO_2			24.3 mEq./L	
Blood serum chlorides			94.7 mEq./L	
Hormonal assay				
Urinary 17-ketosteroids	92.6 mg./24 hrs.	62.4 mg./24 hrs.		
Beta fraction	4.4%			
Urinary gonadotrophin		Neg. at 5 mouse units. (Normal 10-50 m.u./24 hrs.)		
Urinary 11-oxysteroids*		2.92 mg./24 hrs. (Normal 0.30-0.40 mg.)		

*Through the courtesy of Dr. Nathan Talbot of the Massachusetts General Hospital, Boston.

ly succumbed to cardiac failure and pulmonary edema on the fifth postoperative day.

PATHOLOGY

A COMPLETE autopsy was performed three hours after death. Only those findings which seem pertinent are included in this report. Both pleural cavities contained fluid. The lungs were congested and edematous. The ribs were fragile; bands of callus were present at the sites of old fractures, while two ribs on the right showed more recent fractures. The heart weighed 360 gm. and was both hypertrophied and dilated. The liver, spleen and pancreas were essentially normal. The kidneys were normal in size; on microscopic examination they showed capillary congestion and occasional small intratubular calcifications. The brain was normal both macroscopically and microscopically. Careful examination of the hypothalamic area disclosed no abnormality.

Endocrine glands—The surgical specimen consisted of an adrenal tumor, weighing 280 gm. and measuring 10 by 8 by 7 cm., which was completely encased in a firm, fibrous capsule. On hemisection the bulging tumor tissue was deep orange-yellow in color and firm, rubbery and homogeneous in consistency. The tumor cells were extremely large, the nuclei pleomorphic and the cytoplasm foamy and vacuolated. Occasional tumor cells were seen within the capsular connective tissue; in one section these cells were seen in the media and adventitia of a large blood vessel. The pale yellow right adrenal was atrophic; it weighed 3.9

TABLE 2

PREOPERATIVE AND POSTOPERATIVE THERAPY, CASE 1

	DATE	CORTICAL EXTRACT	FLUID INTAKE	OUTPUT	OTHER THERAPY AND REMARKS
PREOPERATIVE	Oct. 31*	25 cc. i.m.			
	Nov. 1	30 cc. i.m.			
	Nov. 2 *Surgery*	20 cc. i.m. 65 cc. i.v.	1200 cc. saline i.v. 1100 cc. 5% glucose in distilled water i.v. 500 cc. blood i.v.	1,560 cc.	Morphine sulfate 0.01 gm. Scopolamine 0.0007 gm. Hykinone 4.8 mg. Ascorbic acid 100 mg.
	After Surgery				Pulse 96; resp. 24; B.P. 152/100. Codeine (subcut.) for pain
	Nov. 3	60 cc. i.v.	2000 cc. 5% glucose in distilled water i.v. 500 cc. blood i.v. 300 cc. saline i.v.	730 cc. urine 450 cc. by thoracentesis	Oxygen Temp. 38° C. B.P. 138/70; 115/65
	Nov. 4	25 cc. i.v.	600 cc. per os 1000 cc. 5% glucose in distilled water i.v. 1000 cc. 5% glucose in saline	750 cc. urine 300 cc. by thoracentesis	Oxygen CO_2 inhalations Amm. chloride Crysticillin 300,000 u. i.m. B.P. 140/90; pulse 118 irregular ECG abnormal; no characteristic pattern
	Nov. 5	15 cc. i.v.	870 per os 1000 cc. 5% glucose in distilled water i.v. 500 cc. saline (subcut.)	450 cc.	Oxygen Prostigmine Crysticillin 600,000 u. i.m. Sulfadiazine 1.5 gm. Severe dyspnea B.P. 115/50; pulse irregular
	Nov. 6	5 cc. i.v.	690 cc. per os 2000 cc. 5% glucose in distilled water i.v.	Urinary retention 500 cc./catheter	Crysticillin 300,000 u. i.m. Sulfadiazine 1.5 gm. Digitoxin 0.4 mg., twice Moist rales bilaterally
	Nov. 7	10 cc. i.v.			B.P. 70/40 Expired of pulmonary edema

*Surgery scheduled for November 1 was postponed one day.

FIGURE 3a and b. Note buffalo-type obesity, with protuberant abdomen, thin extremities and abdominal striae. Ecchymoses also are apparent in antecubital fossae and medial aspect of left thigh.

gm. The orange-colored remnant of the left adrenal weighed 1.5 gm. Microscopically, the right adrenal showed a well formed zona glomerulosa and zona fasciculata. The zona reticularis seemed slightly widened at the expense of the fasciculata. The remnant of the left adrenal appeared normal, as did the medullary layer in both glands.

The pituitary weighed 0.710 gm. The three cell types of the anterior lobe were distributed fairly evenly. The basophils showed the typical hyaline and vacuolated cytoplasm described by Crooke.[2]

The thyroid weighed 8.5 gm. and contained small or medium sized follicles filled with colloid and lined by cuboidal or flat epithelial cells. The isthmus contained a fibrous white nodule which, microscopically, was papillary in nature. The nuclei of the cuboidal cells were hyperchromatic, markedly pleomorphic and showed occasional mitoses.

A parathyroid gland, measuring 1.0 by 0.4 by 0.3 cm., on microscopic examination was seen to be composed of cords and sheets of principal cells only.

The ovaries measured about 2 cm. in length and contained only few and scattered primary follicles.

Diagnosis: Malignant adenoma of left adrenal cortex.

Case 2—Six months after the experience recounted in Case 1, a 32 year old man with similar symptoms of Cushing's syndrome was found to have an adrenocortical tumor.

R. M. was first seen at the University of California Outpatient Department on June 13, 1949, because of reported hypertension. He had been entirely well until four years previously, when he first noted excessive fatigability, with weakness in the lower extremities. This was followed by an insidious gain in weight, especially in the abdomen and face. He complained of frequent attacks of "pleurisy" during the past two years, which were actually the result of multiple fractures of the ribs. The patient first noted intermittent swelling of ankles and legs and puffiness about the eyes one year before coming under our observation. At this time high blood pressure was found. An episode of hematuria of several days' duration had occurred before his admission to the hospital. Although libido had continued unimpaired, potency had gradually diminished.

On examination, the disproportion between the obese trunk and the spindly extremities was striking. The skin was remarkably thin, and large purplish striae were seen over the lower abdomen and hips bilaterally (Figure 3a and b). Many small ecchymoses were scattered over the entire body. The face was rounded and puffy, and the eyes were prominent. The rib cage was tender to palpation, and several nodules of callus about fractured ribs (subsequently verified by roentgenograms) could be felt. The heart was enlarged to the left; the blood pressure was 220/140. The abdomen was protuberant. There was pitting edema of both ankles which extended to the mid-calf of the leg.

Results of laboratory tests are recorded in Table 3, column 1. An electrocardiogram showed an abnormal record of the type associated with left ventricular hypertrophy. An x-ray film of the skull showed an uneven mottled appearance (osteoporosis); the sella turcica was not unusual. Retrograde pyelograms showed no dis-

FIGURE 4a. Perirenal gas insufflation illuminating tumor of right adrenal. b. Lumbar spine showing radiolucency of vertebrae and wedging of first lumbar vertebra.

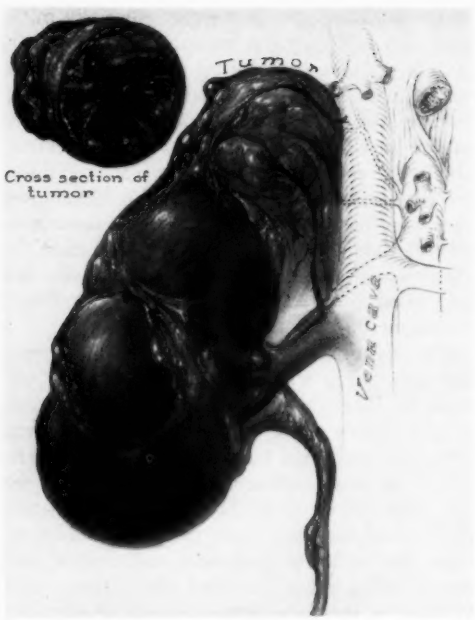

FIGURE 5. Artist's drawing of tumor in situ.

placement of the kidneys, and no definite mass could be identified in the region of either adrenal. Perirenal carbon monoxide insufflation disclosed a small mass, 3 to 4 cm. in diameter, over the upper pole of the right kidney. This was interpreted as a probable adrenal tumor (Figure 4a and b).

In preparation for operation, the patient was digitalized and given a low sodium diet, with ascorbic acid and rutin supplements. It was clear that this was a patient who was rapidly breaking down protein tissue and that he required protein and potassium in order to form protoplasm. Testosterone was given, therefore, in a dose of 50 mg. daily by intramuscular injection to accelerate this formation. Immediately before operation the therapeutic regimen had to be modified considerably, as prophylaxis for addisonian crisis. The testosterone was continued, the potassium was discontinued, and the sodium loss was replaced. Lipo-adrenal extract was given 48 hours before operation, concurrently with desoxycorticosterone acetate in oil, in the hope of preventing a deficiency condition. Five days after treatment with testosterone was begun and three days before operation, the serum carbon dioxide-combining power was 35 mEq. per liter, potassium 2.9 mEq. per liter, and nonprotein nitrogen 43 mg. per cent. No significant retention of salt and water was manifested clinically during the time the patient was taking testosterone.

OPERATION

Since the site of the tumor had been localized, a lumbar approach was preferred, inasmuch as the tumor lay at the level of the rib margin and this approach offered the most exposure with the least hazard to the patient. The eleventh rib was resected after separation from the periosteal sheath. Because of the extreme osteo-

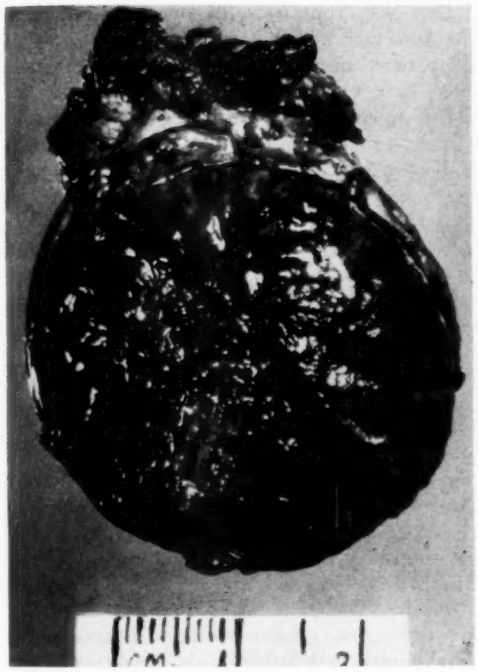

FIGURE 6. Appearance of cut section of tumor.

FIGURE 7. Microphotograph of surgical specimen, including adrenocortical carcinoma (below) and atrophic adrenal cortex (above). Entire thickness of adrenal cortex is represented by area between arrows.

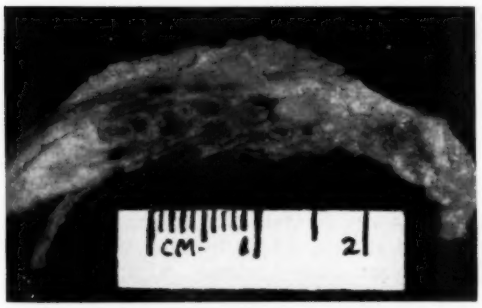

FIGURE 8. Postmortem specimen of left adrenal, including large hemorrhagic infarct (dark portion).

porosis, it was easily straightened by hand and readily cut with suture scissors. The tumor was exposed and was seen to be attached to one pole of a small but otherwise normal-appearing adrenal, most of which stretched over one surface of the tumor. The entire mass was removed easily, with little manipulation or bleeding (Figure 5).

During the operation 500 cc. of whole blood, as well as sodium chloride and citrate solutions, were given intravenously.

The first four days of the postoperative course were relatively uneventful. The patient's blood pressure progressively declined from previous hypertensive levels to approximately 120 to 110/80 to 70, but there was a constant tachycardia of 110 to 130. Fluid and food were well taken and retained; ambulation was instituted on the second day. A total of 340 cc. of whole aqueous adrenal extract was given intravenously during the first four days. Once, on the third postoperative day, the blood pressure dropped to 90/70; response to the intravenous administration of 30 cc. of whole aqueous adrenocortical extract was prompt. The blood chemical values on the fourth day after operation were exactly normal (Table 3, column 3).

During the entire postoperative period, the patient was seen at two hour intervals by both the urologic surgeon and the metabolic internist. On the night of the fourth day, while the tachycardia of about 130 persisted, the patient developed muscular twitching and fibrillations which were generalized. He became irritable and restless. A blood transfusion was started, but was discontinued when a chill supervened. Early in the morning of the fifth postoperative day, he

developed gasping respiration. Suddenly the patient went into profound shock and, despite the intravenous injection of whole aqueous adrenal extract and salt solution, died.

PATHOLOGY

The surgical specimen was a right adrenal tumor, measuring 3 cm. in diameter. It was orange in color and streaked with black (Figure 6). The tumor was partially covered by a thin fibrous capsule and fat. A narrow strip of firmer orange tissue lay above the central tumor nodule and was separated from it by a narrow zone of soft gray tissue. Microscopically, it showed cords of large cells, most of which were clear and foamy, with nuclei of varying sizes (Figure 7). The diagnosis was carcinoma of the right adrenal cortex.

The left adrenal was atrophic, with dimensions of 6.5 by 2 by 0.8 cm. and a weight of only 2.5 gm. It was extremely friable and completely embedded in fat. Two thirds of the entire left adrenal was infarcted (Figure 8). In this area the normal architecture was replaced by soft, friable, dark red material. The remaining third showed a thin, slightly pale but fairly well demarcated cortex and medulla. The microscopic appearance of the structure of two thirds of the adrenal substance was characterized by massive degeneration associated with slight infiltration of chronic inflammatory cells. There was a nearby venous thrombosis and the arterioles showed some thickening and slight hyalinization. A small free clot was found in the central vein. The remaining third of the parenchyma showed edema and focal cortical vacuolization which disrupted the zonal architecture. The anterior lobe of the pituitary was slightly edematous and showed prominent basophilic cells, some with hyaline changes (Crooke's cells). The middle lobe showed excessively large colloid cysts.

The other endocrine glands disclosed no abnormalities. The testes and prostate gland appeared normal. The thyroid lobules were somewhat separated by clear spaces, presumably edema fluid, and the follicles showed slightly more than the normal variation in size. The pancreas exhibited the usual postmortem changes in the acinar cells, but the islets, although few in number, were well preserved and free of fibrosis or hyalinization. The thymus could not be located.

Case 3—In contrast to the preceding two cases, the third case was characterized by the youth of the patient and the short duration of the illness.

P. S., a white girl, 12 years and 11 months old, complained of an excessive gain of weight (from 95 to 130 pounds) and a sudden growth of hair over her entire body during the preceding four and one-half months. Her parents and four siblings were in good health.

Her first menstrual period had occurred five months previously. A second period occurred four weeks later, following which amenorrhea supervened.

THE patient had a full, florid face, marked by acne (Figure 9). Her voice was deep. She was obese; her shoulders and posterior cervical region were particularly heavy, giving her a somewhat "buffalo" appearance. Numerous bluish striae were seen on the upper portion of the thighs. A considerable excess of body hair was present, as well as a downy beard and mustache. The pubic escutcheon was feminine in type, and the clitoris was not enlarged. Breast development was that of early adolescence. The blood pressure varied between 160/60 and 120/80.

Laboratory examination revealed a fasting blood sugar of 83 and 112 mg. per cent, and a normal red blood cell count and hemoglobin. Urinary assay, performed in the laboratory of Dr. Nathan Talbot, showed a 24 hour 17-ketosteroid excretion of 14.7 mg. (alpha fraction, 12 mg. and beta fraction, 2.4 mg.). The bone age was 14½ years; osteoporosis was not apparent roentgenographically. Although retrograde pyelograms showed no abnormality, a plain film of the abdomen showed the shadow of a rounded mass about 5 cm. in diameter above the left kidney. A presumptive diagnosis of tumor of the left adrenal gland was made.

The patient was operated upon by Dr. Donald R. Smith. No unusual preoperative precautions were taken. A tumor, the size of an apple, was found in the region of the left adrenal gland (Figure 10). It was easily freed from the surrounding tissues and was removed through a posterior lumbar incision. Microscopic examination proved it to be an adenocarcinoma, which apparently had not grossly invaded the adjacent tissues.

The pathologist's report follows: "The specimen weighs 51 gm. and measures 7 by 4.5 by 3

FIGURE 9 *(left)*. Patient four and one-half months after onset of obesity, hirsutism, striae and other signs of Cushing's syndrome.

FIGURE 10 *(above)*. Adenocarcinoma of left adrenal gland showing solid, translucent and cellular tumor, with cleavage plane making surgical removal less difficult.

cm. The surface is brown and homogeneously soft. A portion of the capsule is present in one area. On cut section, the tumor is uniformly brown in color and moderately vascular. No definite layers can be recognized, and no hemorrhage, necrosis, or infiltration is present. Microscopically, the entire section is composed of adrenocortical cells of various sizes and shapes. Most of these are irregularly placed and without pattern, although a few of the cells tend to be arranged in rows. The cytoplasm of the abnormal cells is finely granular, somewhat eosinophilic, and contains lipoid vacuoles. Some of the cells are extremely large and have very large, irregular, polychromatophilic nuclei. These nuclei, which are often multiple, contain many round, basophilic nucleoli and show scattered mitotic figures, as well as much pyknosis."

The patient was given 600 cc. of Ringer's solution by hypodermoclysis during the operation. During the first 14 hours after operation, she received 1000 cc. of 5 per cent glucose in normal saline solution by hypodermoclysis and 500 cc. of water by mouth. Vasopressin was given for distention, and morphine sulfate twice for pain and restlessness. During the immediate postoperative period, the patient's condition was relatively stable, but in the following 24 hours her pulse became more rapid and the blood pressure fell slightly. She complained of occasional dizziness. The plasma chloride level was 89 mEq. per liter. It was believed that these signs were due, in part, to adrenal insufficiency. Adrenocortical extract was given intramuscularly in doses of 1 cc. every four hours, and 1 to 2 gm. of sodium chloride orally every eight hours. She received 600 cc. of fluid by mouth and an additional 500 cc. of normal saline solution by hypodermoclysis.

Thereafter, the patient did well. Adrenocortical extract was discontinued on the fifth day, and sodium chloride on the eighth day. The patient was discharged from the hospital 13 days after operation. Three months later, she weighed 111 pounds, 19 pounds less than at the time of operation. It was no longer necessary to remove facial hair, and her voice seemed higher in pitch. Five months after the tumor was removed, she began to menstruate. A year after the operation (Figure 11), she presented a normal feminine appearance. Striae, the sole remaining vestige of Cushing's syndrome, were beginning to fade. Urinary assay, when the patient was 15 years old, showed a 17-ketosteroid excretion of 9 mg. per 24 hours.

The patient has remained in good health.

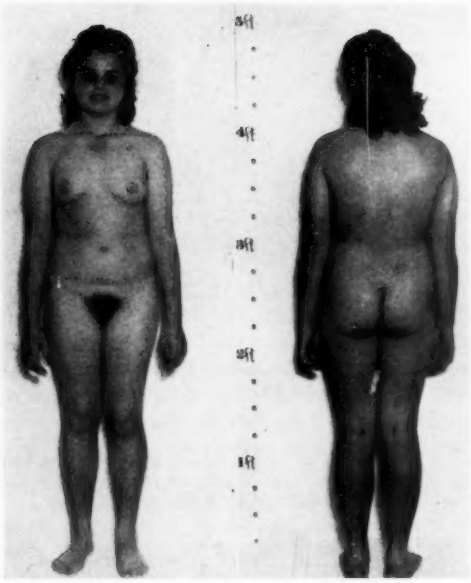

FIGURE 11. Patient 12 months after removal of the adrenal tumor. Obesity, hirsutism and all signs of Cushing's syndrome, except striae, have disappeared.

Eight years after the operation (October 1950), there was no evidence of recurrence. At that time she was 21 years old, 5 feet tall, and weighed 110 pounds; her menstrual periods were regular.

DISCUSSION

In reporting these 3 cases, emphasis is placed on the difficulties of diagnosis, localization and therapy, as well as upon the high surgical mortality attendant upon removal of the adrenocortical tumor in Cushing's syndrome.

THE first case illustrates the difficulties encountered in diagnosis. This patient, in contrast to the patients in Cases 2 and 3, did not conform physically to the classical description of Cushing, viz., no obesity, concealed hirsutism, no striae. Therefore, the correct diagnosis eluded careful, well informed physicians for at least two years, while the patient was labelled a psychoneurotic. The most striking symptoms in patients 1 and 2 were (1) weakness out of all proportion to the physical appearance, this weakness having a predilection for the muscles of the lower extremities, and (2) an excessive appetite characterized by special craving or avidity for protein. In patient 1, to these two symptoms add amenorrhea, hirsutism, acne, easy bruisability and the findings of a full, dusky face, disproportionately thin extremities, hypertension, generalized osteoporosis, pathologic rib fractures, impaired carbohydrate tolerance, high content of 17-ketosteroids and 11-oxysteroids in the urine, and a low circulating eosinophil count, and the picture is complete.

The difficulties of localization of the tumor are exemplified in both Cases 1 and 2. In Case 2, the size of the tumor was such that there remained considerable doubt in the minds of some as to whether a tumor actually had been demonstrated. In Case 1, the tumor, despite its relatively large size, defied detection until perirenal gaseous insufflation revealed its presence. Gaseous insufflation is a valuable procedure, but it is not without risk; in the past it has resulted in the patient's death from air embolism or shock. For this reason, we believe it should be reserved for cases in which the clinical suspicion of tumor is strong. We believe, however, that preoperative localization is of great advantage to the surgeon and the patient, as it eliminates the necessity of manipulating and perhaps traumatizing the contralateral adrenal on whose functional integrity the future of the patient depends. In our patients, perirenal insufflation was carried out under manometric control. Repeated recording of the blood pressure and constant auscultation of the cardiac area were additional safeguards. Both patients tolerated the procedure very well, experiencing only slight thoracic distress for a short period afterward.

Naturally, the high surgical mortality in our series (2 of 3 patients) was discouraging. The records of treatment, before, during and after operation are outlined in detail. Because of the hypertension and cardiac damage in patient 1, desoxycorticosterone was not used for fear of producing fluid retention. Nevertheless, patient 1 died from pulmonary edema and cardiac failure. Clinically, it was extremely difficult to determine the transition from pleural effusion and atelectasis due to surgical trauma to pleural effusion due to cardiac failure. Undoubtedly the delay in the use of digitalis was due to this fact. At no time was there evidence of adrenal failure or of potassium deficit.

TABLE 3

LABORATORY DATA, CASE 2

	PREOPERATIVE 6/23-26/49	PREOPERATIVE 7/8/49	POSTOPERATIVE 7/13/49
Blood count			
Hemoglobin	16 gm.		
RBC	6,000,000		
WBC	14,300	14,200	18,600
Lymph.	16%	20%	
Hematocrit	52%		41%
Sed. rate (Wintrobe)	9 mm./hr.		
Wassermann test (blood)	Negative		
PSP excretion	29%/2 hrs. 65%/2 hrs. (after digitalization)		
Urine			
Sp. gravity	1.009		
Reaction	6.0		
Albumin	+		
Glucose	0		
Microscopic	Occasional hyaline casts, occasional RBC, 2-3 WBC per HDF		
Blood chemistry			
Oral glucose tolerance Test (method of Somogyi)			
Fasting	68 mg. %		
½ hr.	136 mg. %		
1 hr.	204 mg. %		
2 hr.	112 mg. %		
3 hr.	58 mg. %		
Nonprotein nitrogen	62 mg. %	43 mg.%	50 mg. %
Blood serum Na	143 mEq./L	147 mEq./L	141 mEq./L
Blood serum K	3.5 mEq./L	2.9 mEq./L	4.0 mEq./L
Blood serum CO_2	29.6 mEq./L	35 mEq./L	26.7 mEq./L
Blood serum chlorides	94.4 mEq./L	100.5 mEq./L	99.5 mEq./L
Hormonal assay			
Urinary 17-ketosteroids (total neutral steroid)	13.6 mg./24 hrs.		

Patient 2 died of an unfortunate and apparently infrequent complication, infarction of the remaining adrenal gland, despite the fact that trauma to this gland had been avoided deliberately. Dr. A. P. Forbes of the Massachusetts General Hospital has informed us of a like disaster in a similar case.[3] Our patient had been maintained in normal chemical balance throughout; nevertheless the outcome was fatal. This may have been due in part to the precipitous drop from the previously high level of blood pressure in a patient whose blood was more than usually viscous because of the associated polycythemia. It was recognized from the outset that he was a hypertensive patient with congestive failure and that operation would expose him to the hazard of addisonian crisis. It is obvious that the treatment for the one condition is in diametric opposition to the treatment for the other.

It must be recalled that at the time of this operation, cortisone and ACTH were not generally available. Presumably, the bulk of the metabolic deficiencies which result from sudden cessation of the production of excessive 11-oxysteroids could be prevented now by use of either cortisone or ACTH. Of these, ACTH seems the more desirable, since it does not have the inhibitory effect of cortisone on the remaining and already atrophic adrenocortical tissue. It is of interest that this suggestion was made by Cahill and associates as early as 1942.[4]

The third case in our series is of interest because, despite the fulminating development of

the syndrome and the malignant character of the tumor, the patient is alive and well more than eight years after operation. This is the longest *recorded* survival after removal of an adrenocortical tumor associated with Cushing's syndrome.

The remarkably uneventful postoperative course of this patient is in definite contrast to that of the first two patients. Could it be that the specific preoperative measures undertaken in the first two cases actually defeated their purpose by intensifying contralateral adrenocortical atrophy? Or, is it possible that the relatively short duration of the disease and the youth of patient 3 were factors favoring her recovery? In an attempt to find the answers to these questions, the statistical study in the second part of this paper was undertaken.

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Fertility in Men and Women; The How and Why of Having Children. By James Alan Rosen, M.D., Attending Obstetrician and Gynecologist, Lincoln Hospital, New York, New York. Edited with an Introduction for Health Series by Harry Swartz, M.D. 177 pages. 1952, Coward-McCann, Inc., New York. $3.00.

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MORTALITY IN SURGICALLY TREATED ADRENOCORTICAL TUMORS

II. Review of Cases Reported for the 20 Year Period 1930–1949, Inclusive

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THE grave consequences of operative intervention in Cushing's syndrome due to adrenocortical tumor, in our own experience as well as in that of others, prompted a review of reported cases of adrenocortical tumors in an attempt to evaluate the factors that favor survival. The review is restricted to the 20 year period from 1930 to 1949 (inclusive), since prior to that period potent adrenocortical extract was not generally available for prevention or control of postoperative adrenocortical insufficiency. The experience at this University for the same period was similarly reviewed. This study seems particularly timely as a basis for subsequent comparison as we enter the new era of cortisone and ACTH.

It has seemed worth while to the authors to compare the operative survival rate of patients with adrenocortical tumors causing Cushing's syndrome with the survival rate of patients with other types of adrenocortical tumors. For this purpose the cases have been classified on the basis of the hormone or hormones produced, following the logical classification of Cahill, et al.[1] Recent experience with pure steroids has made it possible to attribute specific clinical manifestations to distinct groups of hormones. For example, the role of cortisone-like compounds in the pathogenesis of Cushing's syndrome as postulated by Albright[2] has been well documented by the studies of Sprague, et al.[3] In reviewing the cases of adrenocortical tumors, it is possible, therefore, when reports are complete, to classify all but a few on the basis of the known actions of the principal steroids. In order to incorporate newer knowledge and previously unreported types of functional tumors, we have modified the classifications of Cahill, et al.[1] and Kenyon[4] as follows:

Endocrine Classification	*Principal Criteria*
1. Nonhormonal tumors	No recognizable endocrine manifestations.
2. Androgenic tumors	Clinical manifestations identical with those resulting from the administration of testosterone.
3. Tumors with Cushing's syndrome	
a. "Pure" Cushing's	Clinical manifestations identical with those produced by the administration of 11-oxygenated cortical steroids.
b. "Mixed" Cushing's	As in "pure" Cushing's, with additional androgenic effects, such as clitoral hypertrophy or heavy musculature.
4. Estrogenic tumors	Clinical manifestations similar to those resulting from the administration of estrogenic compounds.
5. Mixed androgenic and estrogenic tumors	Clinical or laboratory observations which cannot be accounted for by estrogens or androgens alone, but which can be explained by the admixture of both types of activity.
6. Tumors associated with hypoglycemia	Recurrent episodes of hypoglycemia.
7. Chorionic gonadotrophin-producing tumors	Clinical manifestation: gynecomastia. Laboratory assay: chorionic gonadotrophin in the urine.
8. Tumors, unclassified	Insufficient data for any of the above classifications.

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RAPAPORT

Whenever possible, the hormonal types were classified on the basis of the clinical picture. Clinical bio-assay seemed a preferable method for determining the type of hormone produced, rather than the assay of urinary hormonal metabolites injected into laboratory animals. For example, it is well known that the administration of testosterone propionate may result in excretion of urinary estrogens. It will be noted that estrogenic metabolites were also found in the urine of patients in whom the clinical manifestations were consistent with androgenic tumor. Not all cases were classifiable. When the data were insufficient, the author's diagnosis, if stated, was accepted; otherwise, such cases were recorded as unclassified. It is likely that errors of classification have occurred; even so, the volume of readily classifiable cases reported bulks sufficiently large to offset the relatively small number of possible misclassifications.

Surprisingly, there were few cases reported where the differential diagnosis between nodular hyperplasia and frank tumor proved difficult. Cases in which the diagnosis of tumor was uncertain were not included in this series.

The diagnosis of Cushing's syndrome was subdivided into two classifications, "pure" and "mixed," in order to determine whether pronounced androgenic manifestations modify the mortality after operation. The motivation for this arbitrary division was Albright's thesis[2] that testosterone, by virtue of its anabolic properties, may counteract the "anti-anabolic" effects of 11-oxycorticoids.

The inclusion of the two unconventional categories, "hypoglycemia" and "chorionic gonadotrophin," was necessitated by recent reports of adrenocortical tumors with these dominant hormonal characteristics.

KEY TO TABLES

Each table represents a different hormonal classification. Those cases in which operative removal of the tumor was attempted are grouped together as "Surgical" and may be identified by the letter "S" in the column entitled "Surgery or Autopsy"; autopsy cases are designated by the letter "A."

Each case is identified by the name of the senior author; if reported more than once, only the first report is mentioned.

Symptoms and signs indicative of hormonal influences are listed; their presence or absence is noted by a plus or minus sign, or by N. A plus sign (+) indicates the presence of an abnormal sign or symptom or the presence in excess of a normal phenomenon. A minus sign (−) similarly means the absence of an abnormal sign or symptom or the decrease of a normal function. Normality, when specifically stated for the sign or symptom being considered, is represented by the letter N. A blank indicates that the case report failed to include any reference to the specific function in question.

Laboratory data are dealt with similarly. A plus sign (+) in the column entitled "glucose response" indicates the presence of impaired glucose tolerance or frank diabetes mellitus.

The figures for all urinary hormones (I.U. = international units; R.U. = rat units; M.U. = mouse units; 17-KS = 17-ketosteroids in mg.; 11-oxy. = 11-oxycorticoids in mg.) represent total 24-hour excretion.

The author's pathologic diagnosis was accepted throughout. A report of carcinoma, malignant adenoma or a metastasizing tumor was recorded as "Ca." The designation "Aden." refers to a benign adenoma. In some cases, only the term "tumor" was reported.

When atrophy of the non-neoplastic adrenal cortex was present, it was designated by a plus sign (+). An N in this column indicates a specific statement by the author that the gland was normal.

A plus sign (+) in the column "operative survival" indicates that the patient survived the operative procedure and was alive at least three weeks postoperatively. A minus sign (−) indicates death in this period, and the details are noted in the column entitled "Comments."

ANALYSIS OF CASES

Since our purpose was to assess the factors influencing survival, we tabulated certain factors which might reasonably be expected to play a role. These were: (1) type of hormones elaborated; (2) malignancy; (3) presence of hormonally active metastases at time of operation; (4) condition of remaining adrenal tissue; (5) site of the tumor; (6) use of specific adrenocortical therapy, as well as, (7) sex, age and such other features as might assume importance during the course of the study.

NONHORMONAL TUMORS

(Table 1)

There were 35 patients in this category. Nine of these were diagnosed at autopsy and 26 came to operation. In 24 cases where the outcome was stated, 21 patients, or a total of 88 per cent, survived the operative procedure.

Eight, or 38 per cent, of these 21 patients subse-

quently developed recurrences or metastases, 5 of them within one year. Three patients with metastases were known to have survived two and one-half, four, and five years, respectively.

Among the remaining 13 patients who survived the surgical procedure, 5 were known to be alive at one year, 15 months, two years, six years, and seven years, respectively. The reported follow-up was insufficient, i.e., less than two months, in the other 8 cases.

A surprisingly high incidence of malignancy was noted in this group. Of 34 cases in which the type of tumor was stated, 32, or 94 per cent, of nonhormonal tumors were malignant, while only 2 were benign. The state of the opposite adrenal was described in 5 cases; in no case was atrophy noted.

Of the 35 tumors, 10 were located on the right side and 20 on the left side. Two tumors were bilateral and one was in an aberrant location on the left side. The location of the other 2 was not stated. The possibility that the operative hazard might be increased by the location of the tumor was considered. It was found that in the 21 patients who survived operation, the tumor was located on the left side in 15 and on the right side in 4; in another patient, the location was aberrant on the left side (one not stated). In the 3 known nonsurvivors, the tumors were on the right side.

Specific adrenocortical therapy during the operative period was reported in 3 cases. All 3 patients survived the operative procedure.

There were 20 males and 13 females in this group; in 2 instances the sex was not stated. All the patients except 2 were adults; the two exceptions were boys, one of whom was 10 months and the other 2½ years of age.

The red blood cell count was reported in 19 cases. Despite the high incidence of malignancy, the count was less than 4,000,000 in only 7 cases.

The presence of a mass was mentioned in 25 cases. Localizing pain coexisted with a mass in 11 patients. In 4 patients, pain without a mass was the sole localizing symptom.

ANDROGENIC TUMORS

(Table 2)

THERE were 72 patients with androgenic tumors. Fifty-eight were operated on, and 12 were diagnosed at autopsy. There were 2 patients on whom operation was attempted but resection was not done.

The age and sex incidence of patients in this group was in striking contrast to that of the group with nonhormonal tumors (Figure 1). There were 9 males and 63 females with androgenic tumors. Of the 9 males, all were children between 1 and 10 years of age. Of the 63 females, 34 were instances of pseudosexual precocity occurring before the age of 16 years; 6 more were examples of a similar syndrome in young women aged 16 to 18 years; 23 had the adult "adrenogenital" syndrome and ranged in age from 19 to 60

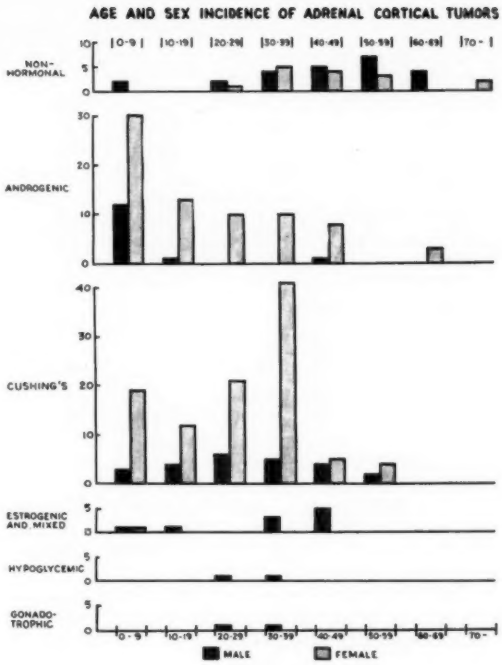


FIGURE 1.

years. There were no cases of the adrenogenital syndrome reported or recognized as occurring in adult males (excluding the case reported from this hospital).

Of the 52 patients in whom the immediate surgical outcome was stated, 37, or 71 per cent, survived the operative procedure, while 15 succumbed. Among the 37 immediate survivors, there were 7 patients (19 per cent) who were known to have succumbed to metastases or recurrence. The reported follow-up was inadequate in the remaining 30 cases of possible cures. One patient, a girl two and one-half years old, was known to have survived at least six years, 5 were known to have survived one to five years, 9 operative survivals were reported less than one year after operation. In the remaining 15 cases, the eventual outcome was not stated.

It occurred to us that, in the case of hormonally active tumors, metastases might also be hormonally active and prevent death from postoperative hormonal deficiency. Accordingly, we correlated survival with the subsequent recognition of metastases or recurrences. In the androgenic group, only 19 per cent of the survivors were known to have metastases or recurrences. Thus, it was concluded that hormonally active metastases were not an important factor in the immediate operative survival of patients in this group.

Of the known 37 patients who survived operation, 19 had malignant tumors, 11 had adenomas; in 7

TABLE I: NON-HORMONAL TUMORS

Number	Reference	Patient Identity	Sex	Age	Habitus	Obesity	Moon Face	Plethora	Striae	Bruisability	Acne	Hirsutism	Voice	Menses	Libido	Phallus or Clitoris	Testes	Breasts	Mental Status	Edema	Blood Pressure	Bone Age	Osteoporosis	Pain	Mass	Miscellaneous Symptoms
1	Culver, H. 1934	Case 1 EC	F	35		Wt. Loss								N						N					+	
2	Shenstone 1936	NW	M	34		-																		+	+	Slightly febrile
3	Frank 1937	Case 3																								
4	CPC Mass. Gen'l Hosp. 1937	23121	F	29		-								Sl. -						+				+	+	Weakness
5	CPC Mass. Gen'l Hosp. 1938	24101	M	43		N														+					+	Rt. tibial metastasis
6	Schill 1939		M	68		-						+								Sl. +						Lost all hair
7	McGavack 1940	Case 5 AT	M	44		-														N				+	+	Vomiting; nocturia
8	Loeb 1941	CS	F	48		-								-						N				+	+	Muscle weakness
9	Mintz 1941	Case 3	F	37		Wt. Loss								-						N					+	
10	Mintz 1941	Case 4	F	42										-						+					+	
11	Joll 1942	NP	M	?		N										N	N			N				+	+	Weakness
12	Cahill 1942	Case 1 AS	F	38										Sl. -						Sl. +				+	+	Weakness
13	Cahill 1942	Case 3 SS	M	36								N			Sl. -	N				N				+		
14	Cahill 1942	Case 5 AK	F	50		-						N						N		N					+	Weakness; anorexia
15	Timoney 1943	SH	F	37		Wt. Loss														N				+	+	Urgency
16	Hoch 1943	Case 2 AF	F	47		Wt. Loss														N				+	+	Pulmonary metastasis
17	Herman 1944	Case 1 VD	M	37																N					+	
18	Bean 1948	Case 3 GF	M	51		+									N					N				+	+	Tarry stools
19	Cottler 1948	BG	F																	+					+	Rectal bleeding
20	CPC-Vancouver Gen'l. Hosp. 1949	Case 4	M	17 mo.																						
21	Walters 1949	I	M	62																M					+	
22	Hyman 1938	Case 10 YL	F	50		-																		+	+	Muscle weakness
23	McGavack 1940	Case 6 EW	F	37		-								-						-					+	Emaciated; lassitude; slightly febrile
24	CPC Mt. Sinai Hosp. 1941	446951	M	44		-														+				+	+	Hematuria; insomnia
25	Tuta 1941	Case 2	M	25		Wt. Loss																				Weakness; hemoptysis; epigastric pain
26	Cahill 1942	Case 4	M																							
27	Burke 1934	Case 1	M	2½																					+	Right abdominal swelling
28	McGavack 1940	Case 4 GM	F	70																N				+		Constipation
29	Tuta 1941	Case 3	M	55																					+	Nausea; vomiting; peptic ulcer

TABLE I: NON-HORMONAL TUMORS

Number	RBC or Hgb	Glucose Response	Androgens	Estrogens	Others	Surgery or Autopsy	Supportive Measures	Type of tumor	Atrophy of opposite adrenal	Metastases	Operative Survival	Comments
1	-					S		Lt. Adr. Ca.			+	Well 6 wks. later
2	-					S		Lt. Adr. Ca.		+	+	Died 8 mos. later with metastasis
3				+		S		Adr. Ca.			+	No endocrine symptoms. Well 2 yrs. later
4	N					S		Lt. Adr. Ca.			+	Well 1 mo. postop.
5	+					S		Lt. Adr. Ca.			+	Postop. course stormy. Well 1 yr. later
6						S		Lt. Adr. Ca.		+	+	Metastasis 4 yrs. later. Pt. developed new hair growth postop.
7	N					S		Lt. Adr. Ca.			+	Tumor inoperable. No follow-up
8	N					S		Rt. Adr. Ca.			+	Uneventful recovery
9	-					S		Lt. Adr. Ca.			+	Exploratory laparotomy. Normal postop. course
10						S		Lt. Adr. Ca.			+	Uneventful recovery
11	N					S	*	Lt. Adr. Ca.		+	+	Died 6 mos. postop. with metastasis. Kidney also removed
12						S	Blood postop.	Lt. Adr. Ca.		+	+	Died 11 mos. postop. with metastasis. No postop. adrenal insufficiency
13						S		Lt. Adr. Ca.		+	+	Received postop. x-ray. Died 2½ yrs. postop. with metastasis. No postop. adrenal insufficiency
14	N					S		Aberrant Lt. Adr. Ca.			+	No postop. adrenal insufficiency
15						S		Rt. Adr. Aden.			+	Non-hormonal. Well 1 mo. later
16						S	Postop. blood, DCA	Lt. Adr. Ca.		+	+	Died 4 mos. postop. with metastasis
17						S		Lt. Adr. Ca.		?	+	Four years postop. developed pain for which chorodotomy done. Apparently well 6 yrs. later
18	-					S	Eschatin	Rt. Adr. Ca.	N		+	Well 15 mos. postop.
19	-					S	Postop.: glucose, saline, blood	Rt. Adr. Ca.		+	+	Had recurrence, but alive 5 yrs. postop. Right kidney also removed. Received x-ray
20						S		Lt. Adr. Ca.		+	+	Died 2 mos. postop. of metastasis
21	-					S	Saline, sodium citrate, cortical hormone, acacia at operation	Lt. Adr. Ca.			+	Developed postop. insufficiency. Was well 7 yrs. later
22						S		Rt. Adr. Ca.			?	Tumor inoperable. No follow-up
23	-					S		Rt. Adr. Ca.	N	+	-	Died 2 wks. postop. Tumor found at autopsy
24	N					S		Rt. Adr. Ca.			-	Died 1 day postop. in shock
25	N					S		Rt. Adr. Ca.	N	+	-	Tumor inoperable. Died 18 days postop.
26						S		Adr. Cort. Tumor			?	Outcome not stated. No postop. adrenal insufficiency
27						A		Rt. Adr. Sarc.		+		X-ray treatment ineffective
28						A		Lt. Adr. Ca.		+		Died in uremia
29	N					A		Lt. Adr. Ca.	N	+		Rt. adrenal 45x20x6 mm.

Number	Reference	Patient Identity	Sex	Age	Habitus	Obesity	Moon Face	Plethora	Striae	Bruisability	Acne	Hirsutism	Voice	Menses	Libido	Phallus or Clitoris	Testes	Breasts	Mental Status	Edema	Blood Pressure	Bone Age	Osteoporosis	Pain	Mass	Miscellaneous Symptoms
TABLE I: NON-HORMONAL TUMORS (Continued)																										
30	Tuta 1941	Case 4	M	32		Wt. Loss												N						+		Nausea; vomiting; dyspnea
31	Howze 1942	RHN	M	51		Wt. Loss									-										+	Fatigue; anorexia
32	Cahill 1942	Case 2 PR	M	58		-					N							N		N						Dyspnea; hemoptysis; pleural fluid with malignant cells
33	Cleveland 1943	WD	M	57		Wt. Loss									N	N				N						Pain in right hip; right illium metastasis
34	Pizzetti 1943		F	74																					+	
35	Alexander 1944	SW	M	49		Wt. Loss																		+	+	Fever
TABLE II: ANDROGENIC TUMORS																										
1	Harris 1930	LS	F	3½		N						+	Deep			+								+	+	
2	Arnold 1934		F	6								+				+										
3	Boeminghausen 1934		F	33				N	+			+		-	-									+		Weakness; abdominal swelling
4	Wharton 1935	Case 4 CS	F	2½		-						+													+	Emaciated
5	Kenyon 1937	GC	F	16								+		-		+				N						
6	Lawrence 1937	Case 1 FH	F	13							+	+	Deep	-		Sl. +						+				
7	Young 1937	Case 20 JM	F	18	Masculine	N			N			+	Masculine	-	+-	+		-	N		N					
8	Ellason 1938	Case 1 NH	F	16	Masculine							+	Hoarse	-		+		-			N					Weakness
9	Friedgood 1938		F	10	Masculine			+	+		+	+	Masculine	+		+					+					
10	Hudson 1938		F	23	Masculine						+	+		-												
11	Greenberger 1941	BK	F	25	Well dev. musculature		N				+	+	Deep	-		+					N			+		Fatigue; visual difficulties
12	Cahill 1942	Case 6 GC	F	16							+	+	Deep	-		+										
13	Cahill 1942	Case 7 RR	F	18	Male							+	Deep	-		+					N					
14	de Jaegher 1942		F	8	Well dev. musculature							+	Deep	+		+		N				12				
15	Luft 1944	Case 5	F	26	Well dev. musculature	+		N	N	N		+		-	-	N		N			N		N			
16	Pratt 1945	Case 1 TP	F	2½	Masculine; Well dev. musculature							+	Deep			+						5				
17	Goldstein 1946		F	8 mo.	Well dev. musculature							+	N			+		N				N			+	
18	McGavack 1946	Case 2 MH	M	5	Increase in ht. Well developed musculature	N						+	Low		+	+						11			+	
19	Flynn 1947	Case 3 CH	F	13	Male							+	Harsh	0		+					N					
20	Hain 1947	Case 3	F	4	Looks older							+				+						12				
21	Hain 1947	Case 5	M	10	Well dev. musculature							+				+	N					12				
22	Johnson 1947	Case 1 ED	F	31		+					+	+		-	-	N					N				+	

Number	RBC or Hgb	Glucose Response	Androgens	Estrogens	Others	Surgery or Autopsy	Supportive Measures	Type of tumor	Atrophy of opposite adrenal	Metastases	Operative Survival	Comments
TABLE I: NON-HORMONAL TUMORS (Continued)												
30	-					A		Lt. Adr. Ca.		+		Tumor tissue negative for estrin and prolan
31	-					A		Bilat. Adr. Ca.				Given x-ray therapy, but rapid downhill course. Died of chronic adrenal insufficiency
32						A		Rt. Adr. Ca.		+		No postop. adrenal insufficiency
33	-					A		Bilat. Adr. Ca.		+	-	Died 48 hrs. postop. in shock with high fever following biopsy of right iliac bone
34						A		Lt. Adr. Ca.				"Pulmonary death"
35	-					A		Lt. Adr. Ca.	N	+		
TABLE II: ANDROGENIC TUMORS												
1						S		Lt. Adr. Ca.		+	+	Well 10 mos. later; Goldstein reported patient's death
2						S		Adr. Ca.		+	+	Died 1½ yrs. later with metastasis
3						S		Lt. Adr. Ca.		?+	+	Recovered. One yr. later, developed edema suggestive of recurrence
4	-					S		Rt. Adr. Hypernephroma			+	Author stated "sexual precocity." Had preop. x-ray treatment
5						S		Lt. Adr. Ca.			+	Good recovery. Also reported by Kurzrok
6						S	Eschatin 3 days	Rt. Adr. Tumor			+	Pelvic exploration neg. Adrenal resection 5 yrs. later. Well 1 yr. later
7	N	± po	<3.3 RU	Prolan A Ø·5 RU		S	Postop.: blood, saline	Lt. Adr. Adeno.	N		+	Well 6 mos. later. Serum sodium was 160 meq. Also reported by Howard, 1937
8	N					S	Postop.: cortin, saline	Rt. Adr. Tumor			+	Well 1 yr. later
9	+		166 mgm 17-KS			S		Adr. Ca.			+	
10			+	+		S		Rt. Adr. Tumor			+	Recovered
11		N	<100 CU	¢00 MU	AZ neg.	S	Preop.: Eschatin; p.o. Eschatin, saline, glucose	Rt. Adr. Ca.		+	+	No postop. shock. Recurrence 9 months postop.
12	N	N	480 IU	8 RU		S		Lt. Adr. Tumor	+		+	No p.o. insufficiency. Well 4 yrs. p.o.
13	N	N	190 IU	33 RU		S		Lt. Adr. Tumor			+	No postop. insufficiency. Recovered
14						S		Rt. Adr. Ca.			+	Died suddenly 1 mo. postop. in shock
15		N	27 mgm 17-KS	28 IU		S		Lt. Adr. Tumor	N		+	Living 1 yr. later
16	N		None	None		S		Rt. Adr. Ca.	N		+	Well 6 yrs. later
17	-					S	Postop.: small doses of cortin	Rt. Adr. Ca.		-	+	Developed postop. atelectasis. Well 1½ yrs. postop.; no evidence of metastasis
18						S		Lt. Adr. Ca.		+	+	Died 3 yrs. later with metastasis
19			1080, 837 mgm 17-KS			S	Preop.: saline, sodium citrate. p.o.: blood, saline, glucose	Rt. Adr. Aden.	N		+	Well almost 2 yrs. later
20	N	N	320 mgm 17-KS	< 5 MU		S		Lt. Adr. Aden.			+	Alive 3 wks. postop.
21						S		Lt. Adr. Tumor			+	Laparotomy performed at age 5. No attempt at removal
22			75 mgm 17-KS			S		Rt. Adr. Ca.			+	No postop. insufficiency. Well 1 yr. later

TABLE II: ANDROGENIC TUMORS (Continued)

Number	Reference	Patient Identity	Sex	Age	Habitus	Obesity	Moon Face	Plethora	Striae	Bruisability	Acne	Hirsutism	Voice	Menses	Libido	Phallus or Clitoris	Testes	Breasts	Mental Status	Edema	Blood Pressure	Bone Age	Osteoporosis	Pain	Mass	Miscellaneous Symptoms
23	Johnson 1947	Case 2 MS	F	2								+				+					N	N				
24	CPC St. Louis Childrens Hosp. 1947	DZ	F	18 mo.	Increased growth	+						+	Husky			+		N				N				
25	Bean 1948	Case 2 IL	F	26		N						+	Deep	-		+		N			N					
26	Gülzow 1948		F	23	Masculine; Well dev. musculature	N			N			+	Deep	-	N	+		-	Depressed		N					Weakness
27	Leahy 1948		F	1								+				+					N	N	N			
28	Weber 1948	PP	M	4	Well dev. musculature						+	+				+					+	N			+	
29	Wilkins 1948	Case 2 TC	F	5½	Well dev. musculature						+	+	Deep			+						7				
30	Cahill 1949	Case 1 ERS	F	7	Well dev. musculature							+	Deep			+			Shy		N	10				
31	Cahill 1949	Case 2 MEH	F	7							+	+	Deep			+		N	Shut-in		N	12				Folyphagia
32	Cahill 1949	Case 4 FH	M	6½	Well dev. musculature						+	+	Deep		+	+	N		Agressive		N	10				Headache; dizziness
33	Higgins 1949		F	1½	Increased growth							+														
34	Kiefer 1949	AB	F	17		Sl.+						+		-		+		N			-		N			
35	Sosman 1949	LB	F	30	Well dev. musculature	+					+	+		-	-	+			Irritable Restless		N	2+	N			Fatigue; headache; blurred vision; exophthalmos
36	Walters 1949	Case 2	F	27		+						+		-				-			N				+	Headaches
37	Walters 1949	Case 3	F	45 mo.			+	+			+	+	Deep			+					N	+			+	
38	Walters 1949	Case 8	F	40 mo.		Sl.+						+				+						N				
39	Schweizer 1930		F	7		+						+				+										
40	Meyer 1931	MR	F	13	Well dev. musculature						+	+		-				N			+			+		
41	Birrell 1932		F	5	Rapid growth	+						+		N		+		N								
42	Rowntree 1933		F	42								+		-				-	Confused	+						Emaciated; ascites
43	Rowntree 1933		F	19		+						+	Coarse								N					
44	Goormatigh 1934	HL	M	6		+			+		+	+	Deep					N								
45	Crooke 1939	Case 2	F	6	Very muscular						+	+				+		N			+	N	N		+	Enlarged abdomen
46	McGavack 1940	Case 3 AM	F	38	Male habitus	-						+	Deep	-	-	+		-			N					Weakness
47	Mellgren 1945	Case 13	F	37		-						+	Deep	+ Then -		Sl. +					N		N			
48	Mellgren 1945	Case 14	F	48					+			+	Deep	-							+					Tiredness; loss of weight
49	Broster 1948		F	14																						
50	Dudits 1935		F	3½	Looks older						+	+	Deep			N			N						+	
51	Kenyon 1937	KP	F	36								+		-		+										

TABLE II: ANDROGENIC TUMORS (Continued)

Number	RBC or Hgb	Glucose Response	Androgens	Estrogens	Others	Surgery or Autopsy	Supportive Measures	Type of tumor	Atrophy of opposite adrenal	Metastases	Operative Survival	Comments
23			78.5 mgm 17-KS			S		Rt. Adr. Ca.			+	Well 6 mos. postop.
24	+	N	45 mgm 17-KS		Pregnanediol 14 mgm	S	DCA, glucose, saline, cortical extract, Lipoadrenal	Lt. Adr. Aden.			+	No postop. insufficiency
25	-	N	93.8 mgm 17-KS	25		S	Eschatin	Rt. Adr. Aden.	N		+	Recovered
26		N				S	Corturone	Lt. Adr. Aden.			+	Bone marrow tissue in tumor. Well 4 wks. later
27			88.8 mgm 17-KS		11-oxy. 1.07 mgm	S		Rt. Adr. Aden.			+	Well 1 yr. later
28						S		Rt. Adr. Tumor	N		+	No adrenal insufficiency postop. Recovered
29	N	N	19,22 mgm 17-KS			S		Rt. Adr. Ca.	N	+	+	Second operation for local recurrence unsuccessful. Died 2 yrs. postop. with metastasis
30			16.4 mgm 17-KS			S	No adrenal therapy	Lt. Adr. Ca.			+	
31	N	N	233 mgm 17-KS	296 mgm		S	Postop.: cortical extract	Rt. Adr. Aden.			+	
32	N		189 mgm 17-KS	296 mgm		S	No adrenal therapy	Lt. Adr. Aden.			+	
33						S		Rt. Adr. Ca.				"Precocious." Well 2 yrs. postop.
34	-	N	88 mgm 17-KS			S	Cortical extract, 2 cc. preop., 60 cc. during and postop.	Rt. Adr. Aden.			+	"Cured."
35	N	N to +	480, 1260 MU		A-Z Test Neg.	S		Lt. Adr. Ca.		+	+	Died 44 days postop.
36		+	241 mgm 17-KS	13 RU		S	Saline, sodium citrate, cortin, DCA	Lt. Adr. Ca.			+	"Adrenogenital syndrome." Alive at least 2 yrs. postop.
37	+		170 mgm 17-KS	16 RU		S	Saline, sodium citrate, cortin, DCA	Rt. Adr. Ca.		+	+	"Adrenogenital syndrome." Died with metastasis 1 yr. later
38	N		6.8, 6.2 mgm 17-KS			S	Saline, sodium citrate, cortin	Rt. Adr. Ca.	+		+	"Mixed picture." Alive at least 9 mos. postop.
39						A		Adr. Tumor				
40						A		Lt. Adr. Ca.	N	+		Died from intra-abdominal hemorrhage
41						A		Lt. Adr. Ca.	N	+		
42						A		Lt. Adr. Ca.		+		
43						A		Adr. Ca.		+		Received x-ray therapy to tumor
44						A		Lt. Adr. Ca.	N	+		Died of intraperitoneal hemorrhage
45	N	N	270 mgm 17-KS			A		Lt. Adr. Ca.		+		Died in heart failure
46	-	N	+	2000 MU		A		Rt. Adr. Ca.	+	+		Died from asphyxia and pulmonary and pleural metastases
47		N				A		Rt. Adr. Ca.	N	+		"No Cushing's"
48						A		Lt. Adr. Ca.	N	+		"No other signs of Cushing's." Author classified as virilism
49		-*				A		Lt. Adr. Ca.				"Adrenal virilism." No other metabolic disturbance * Hypoglycemia
50						S		Rt. Adr. Tumor	N		-	Inoperable. Died 3 days postop
51						S		Adr. Ca.			-	Died postop. in collapse

patients the type of tumor was not stated. Among the 15 patients who died as a result of the operative procedure, 11 had carcinomas, one had an adenoma; in 3 patients the type of tumor was not stated.

Of these 58 surgical patients since 1930, 8 were boys, only one of whom has been reported to be cured (Weber,[5] in 1948) since the first such patient successfully treated by Lisser and Player[6] (see University of California series). The outcome in the case reported by Cahill in 1949[7] was not stated.

The tumors occurred with approximately equal frequency on the right and left sides. In the 72 cases, 31 tumors were on the right side and 33 on the left. One tumor was aberrant in location. In 7 cases, the location was not stated. In this group, in contrast to the nonhormonal group, immediate surgical survival did not appear to be affected by the location of the tumor. In 26 patients with tumors on the right side, in those cases where the immediate outcome was stated, 6 died and 20 survived. Of 22 patients with tumors on the left side (where the outcome was known), 7 succumbed immediately or in the postoperative period, while 15 survived.

Pain and the presence of a mass were infrequent localizing symptoms. A mass was specifically described in 23 patients, of whom 20 came to operation. Of these, 8 patients survived and 9 succumbed immediately; in 3 cases the outcome was not stated. Pain was mentioned in 6 of the 72 cases. Of these 6 patients, 5 were operated upon; 3 survived, while 2 succumbed. Pain and mass coexisted twice; thus pain alone was a localizing symptom in 4 instances. It may be noted that pain and the presence of a mass occurred less frequently in this group of patients than in the nonhormonal group. Undoubtedly in the androgenic group, the striking hormonal manifestations called attention to the adrenal tumor before it was palpable.

Contrary to the general belief that androgenic tumors do not result in atrophy of the opposite adrenal gland, atrophy was present in 7 patients, or 29 per cent, of the 24 cases in which the condition of the opposite adrenal was stated. Twelve patients who came to operation were known to have normal contralateral adrenal cortices. In spite of this, 5 of these succumbed immediately; on the other hand, 5 patients were known to have atrophy of the contralateral adrenal cortices at the time of operation, and of this group, 2 survived the operative procedure. Specific adrenal therapy was given 12 patients, of whom 10 survived and 2 succumbed. Two patients who were reported to have received no specific adrenal therapy survived.

CUSHING'S SYNDROME

(Tables 3-A and 3-B)

THERE was a total of 117 cases of Cushing's syndrome, of which 67 were instances of "pure" Cushing's syndrome, and 50 presented mixtures of Cushing's syndrome with an excessive androgenic component.

Of the 67 patients with "pure" Cushing's syndrome, 39 were operated upon, a biopsy alone was performed in one, while in 27 the diagnosis was established at autopsy. *Of the 39 operated cases, only 18 (47 per cent) survived the surgical procedure.* Of the remaining patients, 20 died and in one the outcome was not stated. Of the 18 who survived the operative procedure, 6 (33 per cent) succumbed later to recurrence or metastases. This left but 12 possible survivors, 3 of whom were known to have been alive more than one year (15 months, 16 months, and four years, respectively). A patient from this hospital who survived eight years is not included in this group.

Once again the question of the possible beneficial effects of secreting metastases upon immediate survival was investigated. Of the 20 nonsurvivors, metastases were reported present at the time of operation in 4 patients, absent in one, and not mentioned in 15. Of the 18 immediate survivors, 6 were reported to have metastases or recurrence. These data were too meager to permit evaluation. Atrophy of the opposite adrenal cortex was found in 19 (73 per cent) of the 26 patients in whom the condition of the opposite adrenal was reported.

The tumor was located on the left side in 34 patients and on the right in 22 patients in the 57 cases in which this information was available. In one patient, the location was aberrant. Specific adrenal therapy was reported in 20 patients, of whom 10 survived operation. In the one case where adrenal therapy was specifically stated to have been omitted, the patient survived. In 20 patients, operation was performed on the left side; of these, 10 survived and 10 succumbed. In 14 cases in which the procedure was performed on the right side, 7 patients survived and 7 did not survive. Thus, apparently location had no influence on immediate survival.

Mass was a localizing feature in 8 patients. Of these, 6 came to operation and 3 survived, while 3 succumbed. Pain, on the other hand, was mentioned as a localizing symptom in 12 patients, only one of whom also presented a palpable mass, so that pain alone was a localizing symptom in 11 patients. Consequently, in at least 19 out of 67 cases, localization might have been accomplished by evaluation of mass or pain. It should be noted, however, that pain may also result from osteoporosis, with vertebral collapse and radicular pain, or from fractured ribs. The converse incidence of the occurrence of pain on the side opposite to the mass was not, of course, usually stated in the case reports.

Of the 19 patients in whom atrophy of the opposite adrenal was noted, 11 were operated upon; only one of these 11 patients survived the operation. In 6 cases where atrophy was specifically noted to be absent, 3 patients came to operation; 2 did not survive. It might be concluded that contralateral adrenal atrophy is an important factor affecting surgical mortality, but such a conclusion must be qualified, since the presence of atrophy is more likely to be discovered if the patient

dies. The administration of specific adrenal therapy was reported in only 10 of the 18 patients who survived operation.

The age and sex incidences are charted in Figure 1. It will be noted that there were 12 males and 55 females in the Cushing's group. Nine of the males were subjected to operation; 4 survived while 5 succumbed immediately. Of the 55 females, 30 came to operation; 14 of these females survived, 15 succumbed, and in one case the outcome was not stated. Thus, sex and age did not appear to influence survival.

We were also interested in determining whether an associated aberration of carbohydrate metabolism might play a role in the excessive surgical mortality of this group. Of the 24 surgical patients with impaired glucose tolerance, 10 survived and 13 died (one, outcome not stated). We were also interested in learning whether the presence of osteoporosis might indicate a more severe degree of protein depletion and, therefore, a worse prognosis. Of the 18 surgical patients in whom osteoporosis was noted, 11 succumbed, 6 survived (one, outcome not stated).

The group of patients presenting the "mixed" Cushing's syndrome with excessive androgenic manifestations was separated deliberately from the group of patients with "pure" Cushing's syndrome in order to determine whether the androgenic and presumably anabolic influence in any way reduced the high rate of immediate mortality. It is of interest that the data for this group are almost identical with those for the group of patients with "pure" Cushing's syndrome. Of the 50 patients with the "mixed" syndrome, 35 were subjected to operation. In the 32 surgical cases in which the immediate outcome of operation was stated, 13 patients (41 per cent) survived, while 19 patients (59 per cent) died. Of the 13 immediate survivors, 7, or 54 per cent, developed recurrences or metastases. *This left 6 possible cured patients out of the entire group.* Only one of these was reported to have survived more than one year. Of the 19 patients who succumbed, 9 were known to have metastases or tumor left behind at the time of operation.

It is of interest to note that of the 13 survivors of operation, 11 harbored a malignant tumor, while only one had a benign tumor (one, not stated). In contrast, of the 19 patients who succumbed, the tumors in 8 were supposedly benign, while in 11 they were found to be malignant.

Youth, at first, appeared to be somewhat of a factor in the surgical survival of this group; 6 of the 13 immediate survivors were less than 14 years of age and one was 19. The one reported known survival of seven years' duration was that of a child 15 months old. In addition, a girl 16 months old was known to have survived nine months. However, a similar incidence of youth was observed in the group of patients who died. Of 18 nonsurvivors, 8 were less than 13 years old and one was 16 years old.

The location of the tumor was almost evenly distributed between the two sides. In 47 cases where noted, 25 tumors occurred on the right side, 21 on the left; in one the origin was aberrant. Of 16 cases of tumors on the left side, in which the outcome was stated, 9 patients died and 7 survived. Of the 15 surgical cases in which the tumor was on the right side, 9 patients died, 5 survived (one, outcome not stated). Thus, the site of occurrence was not a factor in survival after operation.

In the 20 cases where the condition of the opposite adrenal was stated, contralateral atrophy was noted in 14 patients (70 per cent). Of these, 8 came to operation, and only one survived the surgical procedure. Five of the 6 patients without atrophy of the opposite adrenal came to operation; none survived. Once again, there appeared to be a better chance of determining the condition of the opposite adrenal in those patients who died of the operative procedure or came to autopsy. Adrenocortical therapy was specifically mentioned in 10 cases; 6 of these patients survived the operation and 4 succumbed. There were 3 cases in which the treatment consisted solely of the administration of saline and blood and of other supportive measures; all 3 of these patients survived.

In 14 cases the presence of mass was noted. Ten of these 14 patients underwent operation; 5 survived and 5 did not. It would seem that the presence of a mass should mean greater likelihood of not surviving operation, but the rate of mortality appeared to be less in these patients than in the group as a whole. This might be due to the fact that tumors which reach sufficient size to be palpable are probably not very active hormonally. Pain was specifically mentioned in 10 cases, in 3 of which a coexistent mass was noted. Thus, the presence of mass or pain might have provided a means of localization in 21 of the 50 cases, subject to the criticism noted in the section on "pure" Cushing's syndrome.

THERE were 8 males and 42 females in the "mixed" Cushing's group; 2 boys, aged 6½ years and 15 months, respectively, survived the operative procedure; 5 males died (one, outcome not stated). Of the 5 males who succumbed, 3 were children. Twenty-seven of the 42 females underwent operation; 11 survived and 14 succumbed (two, outcome not stated). From these data it would appear that androgenic activity apparently did not protect the patient from operative hazards.

The lack of divergence between the data for the patients with the "mixed" and the "pure" Cushing's syndrome suggests that separation of the patients into the two groups is artificial. Pooling the figures, we arrive at a total of 117 patients with adrenal tumor causing Cushing's syndrome, of whom 74 came to operation. In 70 of these, the immediate outcome is known and 39 (56 per cent) did not survive the operative procedure. Thirteen (42 per cent) of the 31 immediate survivors later succumbed to recurrences or

Number	Reference	Patient Identity	Sex	Age	Habitus	Obesity	Moon Face	Plethora	Striae	Bruisability	Acne	Hirsutism	Voice	Menses	Libido	Phallus or Clitoris	Testes	Breasts	Mental Status	Edema	Blood Pressure	Bone Age	Osteoporosis	Pain	Mass	Miscellaneous Symptoms
TABLE II: ANDROGENIC TUMORS (Continued)																										
52	v. Kup 1937	Case 3	M	3½								+				+	+								+	Enlarged abdomen
53	Ashcraft 1938		F	3½		+					+	+	Bass			+								+	+	
54	Eliason 1938	Case 2 KH	F	5	Coarse features							+	Strong			+			Subnormal						+	
55	da Rocha 1939		F	2							+	+	Hoarse			+									+	Enlarged abdomen
56	Fraser 1940		M	1	Well dev. musculature						+	+	Deep		+	+	N to -		Bad temper			5				
57	Gross 1940	Case 3 LC	M	3								+	Deep			+						6			+	Enlarged abdomen
58	Albert 1941		F	2		-						+				+		N							+	Wasted
59	Cahill 1942	Case 10 IP	F	36		+						+		-		+			Emotionally unstable							Weakness; baldness
60	Kempton 1942	TL	F	15 mo								+	Heavy			+						3			+	Enlarged abdomen
61	Taylor 1942	TLR	M	11 mo								N				+	+		Alert		N				+	Enlarged abdomen
62	Salgado 1943		F	23	N			+			+	+	N	-		+		N	N		N		N			
63	Schultheiss-Linder, 1943		F	42								+	Deep	-		N										Dyspnea; ascites; pleural fluid
64	Flynn 1947	Case 5 NMA	F	31								+		Scanty							N		N	+		Gained weight
65	Dingemanse 1938	Case 1	F	40								+		-							+				+	
66	Dingemanse 1938	Case 2	F	49																						
67	Talbot 1940	Case 9 CH	F	5	Well dev. musculature	N					+	+	Deep			+						10			+	
68	Fraser 1941		F	3½							+	+	Deep			+					N					
69	Luft 1943		F	7		+						+							Apathetic; comatose						+	
70	Hain 1947	Case 6	F	60								+	Deep			+										
71	Samuel 1948		F	12							+	+	Deep								N				+	
TABLE III-A: CUSHING'S SYNDROME																										
1	Cecil 1933		F	31		N		+						-	-	N				+	+			+		Weakness
2	Walters 1934	Case 5	F	37		?+					+	+	Coarse								+		N		+	
3	Lescher 1934/1935	IC	F	35		+		+	+	+		+	N	-		N					+		+	+	+	Dry skin; normal strength
4	Volini 1935	MB	M	23		+		+	+		+				-	-					+		+		+	
5	Assman 1935	Case 3	F	37		+	+	+						-							+		+			
6	Josephson 1936	KIK	M	17		+	+		+			-				-	-	N	-		+		Sl. +	+		Dyspnea; tachycardia; hyperhidrosis; weakness
7	Oppenheimer 1937	Case 3	F	34																						
8	CPC Mass.Gen'l Hosp., 1937	23011	F	36	Shortened stature	+	+	+	+	+		+	Husky	-		N				+	+		+			Headache; blurred vision; kidney stones; heart failure

Number	RBC or Hgb	Glucose Response	Androgens	Estrogens	Others	Surgery or Autopsy	Supportive Measures	Type of tumor	Atrophy of opposite adrenal	Metastases	Operative Survival	Comments
TABLE II: ANDROGENIC TUMORS (Continued)												
52						S		Lt. Adr. Ca.	+		-	Died 10 hrs. postop. Had left ventricular hypertrophy at autopsy
53	-					S	Postop: digitalis; glucose	Lt. Adr. Ca.			-	Died 36 hours postop. Kidney removed with adrenal
54						S		Access-ory Adr. Aden.	N		-	Died 3 hours postop. in shock
55						S		Rt. Adr. Ca.			-	Tumor not removed at surgery. Died 2 days postop.
56			90 IU			S		Rt. Adr. Tumor	N		-	Died suddenly 12 hrs. postop.
57	N					S		Lt. Adr. Ca.			-	Died 2 hrs. postop. in shock
58						S		Rt. Adr. Ca.	N	+	-	Laparotomy only, but died 1 day postop. in shock
59	+		69 IU			S	Postop.: saline; blood; cortin	Rt. Adr. Tumor	+		-	Died 32 hrs. postop. following a convulsion
	N					S		Lt. Adr. Ca.	N		-	Died 12 hrs. postop. in shock
61	N					S		Lt. Adr. Ca.	+	+	-	Died 13 hrs. postop. in shock. Tumor not fully removed
62						S		Rt. Adr. Ca.			-	Received pituitary x-ray, and estrogens postop. Died from hemorrhage
63			6.6 mgm Andro-sterone	5 RU		S*		Lt. Adr. Ca.			-	Pleural metastasis. Androsterone in ascitic fluid. Estrogen in pleural fluid * Laparotomy only
64	N	N	28 mgm 17-KS			S	Preop.: Low potassium, high sodium diet; Eschatin, DCA. Post-op.: blood, saline, DCA	Lt. Adr. Ca.			-	Died 8 days postop. Developed p.o. pyopneumothorax
65			1000 IU	11,000 IU	Prolan Neg.	S		Rt. Adr. Ca.		+	?	Outcome?
66			2200 IU	100 IU		S		Adr. Tumor			?	Outcome? Author called this "virilism." (*Also reported by Bruins Slot, 1936)
67			160 mgm 17-KS			S		Rt. Adr. Ca.			?	Inoperable. No follow-up
68						S		Rt. Adr. Tumor			?	Outcome?
69			155, 132 mgm 17-KS			S		Lt. Adr. Ca.			?	Outcome?
70						S		Adr. Tumor			?	Outcome?
71						S*		Lt. Adr. Ca.				"Adrenal virilism." Tumor inoperable * Punch biopsy
TABLE III-A: CUSHING'S SYNDROME												
1						S		Lt. Adr. Ca.			-	Only part tumor removed. Died 12 hrs. p.o. pulmonary hemorr.
2	N	+				S	Blood, adrenalin, cortin	Lt. Adr. Ca.	+		-	Died 4 days p.o. in coma
3	+	+				S		Lt. Adr. Ca.	N		-	Temp. & pulse rose p.o. Died 12 hrs. p.o.
4	N	+				S		Rt. Adr. Ca.			-	Died 1 hr. p.o. in shock
5		+				S		Lt. Adr. Ca.		N	-	Died of pneumonia p.o. Rt. adr. deficient in lipoid
6	N	N				S	P.o.: cortin, saline, glucose, blood	Lt. Adr. Rest Tumor	Both Adrs.		-	Died 19 hrs. p.o.
7					FSH Normal	S	P.o.: saline, blood, adrenal hormone	Rt. Adr. Aden.			-	"Typical Cushing's." Died p.o. despite normal electrolytes
8	N	+				S		Lt. Adr. Ca.		+	-	Died 3 wks. p.o. during operation for gluteal phlegmon

TABLE III-A: CUSHING'S SYNDROME (Continued)

Number	Reference	Patient Identity	Sex	Age	Habitus	Obesity	Moon Face	Plethora	Striae	Bruisability	Acne	Hirsutism	Voice	Menses	Libido	Phallus or Clitoris	Testes	Breasts	Mental Status	Edema	Blood Pressure	Bone Age	Osteoporosis	Pain	Mass	Miscellaneous Symptoms
9	Lawrence 1937	Case 3	F	30		+		+	+	+		+		-						+	+					Weakness; polyuria
10	Lukens 1937		F	25		+		+	+	+		+		± Irregular		N					+		+			
11	Scholl 1938		F	28		+		+		+		+		-		N					+		+			Weakness; losing hair
12	Elliott 1938		M	24		+		+	+			N			N	N				+	+					Polyuria; polydipsia; lethargy
13	Josephson 1938		F	43								+											+			Had clinic. Addison's Disease.
14	Weinberg 1941	Case 1	F	34		+	+		+			+		-							+		+			
15	Mintz 1941	Case 5	F	30		+		+	+	+	+	+		-		N					+		+			Weakness
16	Humphreys 1942	Case 1	F	47		+			+			+	Husky	-		N					+					Prominent eyes
17	Farber 1943		M	15				+	+			N			-	-		N			+		+			
18	Mellgren 1945	Case 1	F	15		+	+		+			N		-							+		+	+		Headache
19	Mellgren 1945	Case 5	M	37		N	+	+	+												+		+	+		Tiredness
20	Spence 1947	GEB	F	24		+			+		+	+		-	N	N		Sl. +			+				+	Tuberculosis
21	Maddox 1949	WT	F	18		N	+	+			+	+	N	-		N		-			+	18	N		+	Prominent eyes
22	Lightwood 1932		M	18 wks		+	+	+				+				N					+					Pneumonia
23	Ashe 1934		F	3		+	+	+				±				N			Convulsions		+		N		+	Muscle weakness; Polyphagia
24	Lyall 1935		F	30		+		+				+							Left CVA		+					
25	Bettoni 1936		F	27		+						+		-							+					
26	Horneck 1936	Case 2	M	22		+			+						-		-						+			
27	Kenyon 1937	CF	F	31		+					+	+		-							+		+			
28	Tesseraux 1937		F	32	Cushing	+	+	+	+			+		-					Epilepsy	N	+		+			Exophthalmos; galactorrhea
29	Kenyon 1937	PR	F	31		+			+			+		-		N					+					
30	McCavack 1940	Case 1 ET	F	34		+	+		+			+		-		-				+	+		+			muscle weakness
31	Gross 1940	Case 5 BJB	F	3		+										N			Retarded cretinoid facies		+					Convulsions
32	Gross 1940	Case 4 ML	F	10			+	+			+	+				N					+					Muscle weakness; nocturia; abdominal swelling
33	Marks 1940		F	10 mo		+			+			+	Harsh			N					+		N			
34	Fraser 1941	Case 2	F	36		+					+		+	Husky	-						+	+					Chest pain, kidney stones
35	McLetchie 1942		F	26		N		+	N		+	+		-		N		-	Coma		+					
36	Lukens 1942	Case 2	F						+														+			Pulmonary metastasis
37	CPC Mass.Gen'l Hosp., 1943	29321	F	51		+		+	+	+	+	+	Deep			? +		-		+	+		+			Weakness; headaches

TABLE III-A: CUSHING'S SYNDROME (Continued)

Number	RBC or Hgb	Glucose Response	Androgens	Estrogens	Others	Surgery or Autopsy	Supportive Measures	Type of tumor	Atrophy of opposite adrenal	Metastases	Operative Survival	Comments
9	N	+				S	P.o.: adrenalin, Eschatin, glucose, saline	Lt. Adr. Aden.	+		-	Died p.o. with hypotension
10	N	+				S	Fluids, glucose, saline p.o.	Rt. Adr. Aden.	+ Absent		-	Died 8 days p.o.
11	N					S	P.o.: salt, adrenalin, eschatin, oxygen	Lt. Adr. Aden.	+		-	Died in shock 36 hrs. p.o.
12	+					S		Lt. Adr. Ca.	+		-	Died in shock 12 hrs. p.o.
13		+				S		Adr. Tumor			-	Diabetes disappeared for 4 mos. Pt. died p.o. of acute adrenal insufficiency
14		+				S	P.o.: eschatin, plus usual support. meas.	Rt. Adr. Aden.	+		-	Died 1 day p.o. in shock
15	N	+				S	Cort'n p.o.	Lt. Adr. Aden.	+		-	Died 21 days p.o. bronchopneumonia
16		+				S		Adr. Ca.	+	+	-	Died p.o.
17	+	+				S		Rt. Adr. Ca.		+	-	Died 1 day p.o.
18				Less than 17 MU	Prolan >67	S	P.o.: cortin (large amts.)	Rt. Adr. Ca.	N	+	-	Died 1 wk. p.o.
19	+	+	>18 but <55 MU		Prolan A >17 MU	S		Rt. Adr. Ca.		+	-	Died 24 hrs. p.o.
20	N					S	P.o.: oxygen, plasma, DCA, glucose, saline	Rt. Adr. Ca.	+ Absent		-	Died 48 hrs. p.o.
21	N	+	40 mgm 17-KS			S	Blood, saline, eschatin during & after op.	Lt. Adr. Ca.			-	Died 1 day p.o.
22	-					A		Lt. Adr. Aden.				Left ventricular hypertrophy at autopsy
23	+	N				A		Lt. Adr. Aden.				Died in coma
24		+				A		Rt. Adr. Ca.	+			Died 1 day after craniotomy
25		+				A		Adr. Aden.				Adenoma of pituitary
26		+				A		Adr. Aden.				Eosinophile pituitary tumor
27						A		Rt. Adr. Aden.	+			Died in renal and heart failure
28						A		Lt. Adr. Aden.	N			Died of miliary tuberculosis
29		+				A		Rt. Adr. Aden.	+			Died from occlusion of left femoral and external iliac arteries
30	+	+				A		Lt. Adr. Ca.	N			Died of bronchopneumonia
31	N	N				A		Lt. Adr. Ca.				Died in coma
32	N	+				A		Rt. Adr. Ca.				Died of pneumonia
33	+	N				A		Rt. Adr. Adeno-ma				Died in pulmonary edema
34	+	+	19.9 mgm 17-KS			A		Lt. Adr. Ca.		+		
35						A		Adr. Rest. Ca.	Both adr. hyper-plastic			Adrenal rest in tail of pancreas
36						A		Adr. Ca.				"Picture of Cushing's syndrome"
37	N	+	16.8, 10.4, 10.2 mgm 17-KS		FSH Neg. for 3 MU	A		Lt. Adr. Ca.	+	+		Died of mediastinal emphysema

TABLE III-A: CUSHING'S SYNDROME (Continued)

Number	Reference	Patient Identity	Sex	Age	Habitus	Obesity	Moon Face	Plethora	Striae	Bruisability	Acne	Hirsutism	Voice	Menses	Libido	Phallus or Clitoris	Testes	Breasts	Mental Status	Edema	Blood Pressure	Bone Age	Osteoporosis	Pain	Mass	Miscellaneous Symptoms
38	Heinbecker 1944	Case 6	F	28		+	+		+	+	+	+		-	-	N					+		+	+		Apathy
39	Mellgren 1945	Case 3	F	32		+	+		+		+	+		-									+			Tiredness
40	Büchler 1946		F	22		+	+		+	+	+	+	N	-		N		N	Apathetic		+			+		Weakness
41	Hain 1947	Case 1	F	21								+		-							+					
42	Benard 1947		F	30		N	+	+	+	+	+	+		N		N		-	N	+	+				+	Weakness; prominent eyes
43	Abdine 1948		F	38		+						N	N	-				-			+					Pelvic mass
44	Kiefer 1949	JD	F	9 mo.		+					+	+				N					+		N			
45	Schluter 1930		F	33		+								-							+					
46	Graef 1936		F	19		+			+			+									+					
47	Horneck 1936	Case 1	F	13		+			+			+		-							+					
48	Humphreys 1942	Case 2	F	29		+			+			+	Husky	-		N					+		+			Prominent eyes; uremia
49	Shallow 1933		F	27		+						+		Metrorrhagia		N				+	+			+		Muscle weakness polyphagia
50	Walters 1934	Case 3	F	39		+					+	+				N				+	+		+			
51	Walters 1934	Case 4	F	30			+	+				+		-							N					Weakness
52	Walters 1934	Case 1	F	25		+	+		+	+	+	+		-							+					Polyuria; weakness
53	Oppenheimer 1937	Case 2	F	34			+			+		+		-		N					+		+		-	
54	Lawrence 1937	Case 2	F	24				+			+	+		-					Coma		+				+	
55	Walters 1938	Case 5	F	19	Masculine	+	+	+	+		+	N		-		N		+								Weakness
56	Crooke 1939	Case 1	M	25		+		+	+		+	+				N				+	+	N				Muscle weakness
57	Broad 1940	IS	F	30		+					+			-							+			+	+	Weakness
58	Sprague 1943		F	49	N							N		N							+				+	
59	Wilhelm 1944	137160	M	46		+		+	+										Irritable		+		+			Blurred vision; dizziness
60	Callow 1944	Case 1	F	61		+	+	+				+				N		-			+					Weakness
61	McLaughlan 1947		M	44		N	+	N	N		N								Very depressed		+		+	+		Weakness
62	Lewis 1947		M	26	"Typical Cushing"																+		+	+		Urinary stones
63	Flynn 1947	J McG	F	32		+						+									+					Headache; dyspnea; insomnia
64	Walters 1949	Case 7	F	50		+	+	+		+		+									+		+			
65	Walters 1949	Case 4	F	24		+	+	+	+		+	+		N to +							N		N			Weakness; dry skin; polyuria
66	Dingemanse 1938	Case 3	M	34																						

TABLE III-A: CUSHING'S SYNDROME (Continued)

Number	RBC or Hgb	Glucose Response	Androgens	Estrogens	Others	Surgery or Autopsy	Supportive Measures	Type of tumor	Atrophy of opposite adrenal	Metastases	Operative Survival	Comments
38		+				A						Adrenal tumor
39		+	25 mgm 17-KS			A		Rt. Adr. Aden.				Normal left adrenal removed. Died 2 yrs. postop., suicide
40	N	+				A		Lt. Adre. Ca.	+	+		Died of pneumonia with shock. (Had pigmentation)
41	N	+	45 mgm 17-KS	N	Pregnanediol 25 mgm	A		Lt. Adr. Ca.		+		Original left adrenal tumor removed for non endocrine symptoms 3 yrs. before
42	-		+			A	DCA p.o. for shock	Lt. Adr. Ca.	+	+	+	Died following hysterectomy
43						A		Rt. Adre. Ad.			-	
44	N		2.7 mgm 17-KS			A		Lt. Adr. Aden.	N			
45						A		Lt. Adr. Ca.	+	+		
46						A		Adr. Ca. Pituit.				
47						A		Adr. Aden.				
48						A		Adr. Aden.	+			
49	-	+				S		Lt. Adr. Ca.		+	+	Died 5 mos. p.o. with pulmonary metastasis
50		N				S	Eschatin, saline	Lt. Adr. Ca.			+	Recovered
51		+				S	Eschatin	Lt. Adr. Ca.			+	Later died of ca.of pancreas
52						S	Cortin, blood, saline	Rt. Adr. Ca.		+	+	Symptoms & mass recurred 6 mos. p.o.
53		+			Increased FSH	S		Lt. Adr. Ca.		+	+	Died 2 mos. p.o. from metastasis
54		-				S		Lt. Adr. Ca.			+	Oper. 2 times. Both inoperable. Eventually died
55		+-				S	Saline, sodium citrate, cortin	Rt. Adr. Cytoma			+	Symptoms regressed p.o.
56	+		40 mgm 17-KS			S	Cortin, saline, p.o.	Lt. Adr. Ca.			+	Stormy course p.o. Well 4 mos. later
57	N	+				S	Adrenalin, caffeine	Lt. Adr. Ca.		+	+	Recovered from shock 24 hrs. p.o. Dev. local recurr. Died 2 yrs. p.o.
58	N	+				S	None	Rt. Adr. Tumor			+	Diabetes disappeared after op. No adren. insufficiency p.o.
59		+	92.8 mgm 17-KS	1000 IU		S	DCA, testosterone & cortin preop. and postop.	Rt. Adr. Aden.			+	Stormy p.o. Well 16 mos. later
60		+	14.5, 20 mgm 17-KS			S	DCA p.o.	Lt. Adr. Ca.		+	+	Died 2 mos. later with metastasis
61	N	N				S	Preop.: blood. Postop.: Eschatin, DCA, saline, oxygen, blood, amino acids	Rt. Adr. Ca.			+	Well 15 mos. later
62	N	+				S		Rt. Adr. Ad.			+	P.O. received 800 r. each temple. Alive 4 yrs. later
63		N	11.6, 6.5, 15, 13.5 mgm 17-KS			S		Lt. Adr. Aden.			+	Recovered
64	-	+	4.9, 6.7 mgm 17-KS	-		S	Saline, sod. citrate, cortin	Rt. Adr. Aden.			+	Alive 5 mos. p.o. Dev. prob. rheumatoid arthritis
65	N	+	3.5, 7.3 mgm 17-KS	Pos. 60 RU	Prolan Pos. 5 RU	S	Saline, sod. citrate, cortin	Lt. Adr. Ca.			+	Alive 8 mos. p.o.
66			600 IU	110 IU				Adr. Tumor			?	Author called case "Cushing's"

metastases. Contralateral atrophy was searched for in 46 patients and was noted in 33 (72 per cent of these cases). The location of the tumor was stated in 104 cases; the tumor was found on the right side 47 times, on the left 55 times, and in an aberrant site twice.

ESTROGENIC TUMORS

(Table 4)

There were 6 patients in this group, all male. Four came to operation; all survived the procedure. It is to be noted, however, that 3 of the patients subsequently died with metastases, while only one, a boy four and one-half years old, was known to be alive four years after operation. The tumor was stated to be malignant in 3 cases (other 3, not stated). The tumor occurred on the right side in 2 patients and on the left in 2 (2 cases, location not stated). The condition of the opposite adrenal was mentioned in only one case and was considered normal. This patient also survived the operative procedure. A mass was noted in 2 patients. Pain was not specified nor were supportive measures recorded.

MIXED ESTROGENIC AND ANDROGENIC TUMORS

(Table 5)

THERE were 4 patients in this group. Three of them came to operation; in the remaining patient, the tumor was found at autopsy. Of the 3 patients operated upon, 2 survived the procedure (one, outcome not stated). Of the 2 survivors, one died of metastases 11 months after operation (one, follow-up not reported). The condition was discovered in 3 adult males and in one girl 23 months old. In adult premenopausal females, it is likely that such tumors would be recognized only by their androgenic manifestations. A clue to the hormonal type responsible for this syndrome is found in the case of W. W. Scott,[8] whose patient had a large urinary output of dehydroisoandrosterone. This steroid has both androgenic and estrogenic activity.[9]

In all 4 patients in this group, the tumor involved the left adrenal. Three of the tumors were carcinomas; the pathologic status of the fourth was not described. Metastases were present in 3 of the 4 patients.

ADRENAL TUMORS ASSOCIATED WITH HYPOGLYCEMIA

(Table 6)

This group consists of 2 patients. One of them came to operation and a right adrenal carcinoma was removed; the patient survived the surgical procedure but the subsequent outcome is not stated. The second patient died of hypoglycemic shock, came to autopsy, and was found to have a left adrenal carcinoma. Specific adrenal therapy was administered to the patient who survived.

Thannhauser has mentioned 3 additional cases[10] but, unfortunately, too briefly for inclusion in this report.

CHORIONIC GONADOTROPHIN-PRODUCING TUMORS*

(Table 7)

This group is represented by 2 patients, both adult males. One, with left adrenocortical carcinoma, came to operation and survived. (Subsequent outcome not stated.) The other patient came to autopsy, where a right adrenal carcinoma with metastases was discovered. Both patients had palpable masses, but in neither was pain mentioned. No specific adrenocortical therapy was given the patient who came to operation; the condition of the opposite adrenal was not mentioned.

UNCLASSIFIED TUMORS

(Table 8)

Classification of hormonal types of adrenocortical tumors was readily made in all but 16 cases.

UNIVERSITY OF CALIFORNIA SERIES

(Table 9)

Since the University of California cases consist of only 23 patients, breakdown of this series into hormonal groups is of little statistical value. There were 8 patients with nonhormonal tumors, 8 with androgenic tumors, one case of an estrogenic tumor in an adult male, and 5 cases of "pure" Cushing's syndrome; one tumor could not be classified. It is of interest that of the total of 23 patients, the sex incidence was approximately equal, i.e., there were 12 males and 11 females. Of unusual interest is the fact that 3 of the cases of Cushing's syndrome occurred in adult males.

Seventeen patients underwent surgery. Six of these patients had tumors of the nonhormonal type; 3 survived the operative procedure, while 3 did not. Androgenic tumors were resected from 7 patients, and all survived the surgical procedure. This outcome is in striking contrast to that reported in the literature. One of the 7 had metastases at the time of operation and died of these one year later. The follow-up in the other 6 patients with androgenic tumors is as follows: All 6 are known to be alive (2 at two years, 1 at three years, 1 at four years, 1 at 14 years, and 1 at 18 years after the operation). There were 3 patients with "pure" Cushing's syndrome who came to operation; 1 patient survived and 2 died in the postoperative period. The details of these cases are reported in Part I of this paper. The single patient with an unclassified tumor survived the surgical procedure; however, metastases were noted at the time of operation. Of the 23 tumors, 7 were reported benign and 16 malignant. The tumor was found on the left side in 12 of the cases, on the right side in 10; one patient had a bilateral adrenal carcinoma with no hormonal manifestations.

The condition of the opposite adrenal was noted in

*Subsequent to the period under consideration in this study, Reifenstein[11] has reported an additional case.

7 cases; atrophy was present in 3 of these cases, 2 of which were the "pure" Cushing's syndrome and one of which was the surviving patient with a masculinizing syndrome reported by Escamilla and Johnson. In 4 patients the opposite adrenal was normal; one of these patients had an androgenic tumor, one had Cushing's syndrome, which was discovered at autopsy, and 2 had nonhormonal tumors. As found in the cases reported elsewhere, atrophy of the contralateral adrenal occurs with tumors of the hormonal types, androgenic as well as in Cushing's syndrome, in contrast to the nonhormonal types where it has not been found.

Mass was a frequent localizing sign in the nonhormonal group, occurring in 6 of the 8 cases. Four of these patients had localizing pain also. One patient with a nonhormonal tumor had pain without a palpable mass. It was surprising to note that 6 of the 8 androgenic tumors were palpable (one patient also had localizing pain), in contrast to previously reported androgenic tumors which only rarely have been palpable. In the single patient with an estrogenic tumor, mass and pain coexisted. In none of the patients with Cushing's syndrome was the tumor palpable. Localization in 2 was accomplished only through the use of perirenal gas insufflation.

Specific adrenal therapy was used routinely in all patients who underwent operation in this hospital, and adrenocortical insufficiency did not occur in the first three days postoperatively. Despite this, the mortality in Cushing's syndrome was similar to that recorded in the literature, and 2 of the 3 patients who came to operation succumbed. A discussion of the specific effect of therapy in this particular syndrome may be found in the cases described in Part I of this report.

Certain unique features are observed in the University of California series. It is of historical interest that the first successful operation for an androgenic adrenocortical tumor in a boy was that of Lisser and Player.[6] A similar good result was noted in *all* patients with androgenic tumors treated surgically in this hospital, including the case of pseudosexual precocity reported by Reilly, Lisser and Hinman.[12] It has been postulated[13] that recognition of a virilizing syndrome in an adult male would not be possible. Such a syndrome has, however, been recognized and reported from this hospital by Kerr and Gordan.

It seems likely that follow-up reports from other institutions might also disclose long-term postoperative survivals in patients with Cushing's syndrome associated with adrenocortical tumor. However, these must of necessity be very few, in view of the serious surgical mortality and the large number of patients who later succumb to recurrence or metastases. The eight-year survival and presumed cure of a patient with neoplastic Cushing's syndrome reported in detail from this hospital in Part I of this paper is, to our knowledge, the longest follow-up period reported.

Similar long-term survivals are noted in the patients with androgenic tumors in this series. The patient originally reported by Lisser and Player[6] is alive, well, and presumably cured of a malignant tumor of the adrenal cortex 20 years after operation. The patient with pseudosexual precocity reported by Reilly, Lisser and Hinman[12] is presumably cured 14 years following operation. Sufficient time has not yet elapsed to comment upon the other presumed cures in this group. The series from this hospital also points up the fact observed in the literature, that lateralization of adrenocortical tumors occurs at random, and that there is no greater incidence of occurrence on one side than on the other. It is also noted that, while adrenocortical tumors with Cushing's syndrome are quite rare in men, nonetheless, they do occur, as exemplified in the three cases from this hospital.

DISCUSSION

The special problem of the disproportionately high surgical mortality in Cushing's syndrome associated with adrenocortical tumor demands (at the least) separation of the roles played by (1) malignancy, (2) possible beneficial effects that might be expected from androgenic steroids, (3) presence or absence of hormonally active metastases at time of operation, (4) condition of the opposite adrenal, (5) localization of the tumor, (6) specific adrenocortical therapy, and (7) such miscellaneous factors as age, sex and duration of the disease.

As for the factors relating to the technical hazards of removing the tumor itself, the group of patients with nonhormonal tumors serves as a satisfactory control. The fact that this type of tumor is so frequently a carcinoma also serves to indicate that portion of the mortality due to malignancy per se. However, certain reservations exist in the minds of the authors as to the accuracy with which malignancy may be ascertained histologically in adrenocortical tumors. It is not infrequent for metastases to appear in patients in whom the original pathologic diagnosis was benign adenoma. On the other hand, it is encouraging to note the large number of cures in patients in whom carcinoma or malignancy had been diagnosed from the appearance of the original tumor.

From the data on the 26 patients with surgically treated nonhormonal tumors (Table 1), it would seem that the operative mortality from the attempted resection of these tumors, which are usually larger than hormonally-active tumors, is in the neighborhood of 12 per cent. It might be anticipated that androgenic steroids could, by virtue of their anabolic effects, exert a restraining influence upon operative mortality. Such proved not to be the case, for the immediate mortality of the patients with androgenic tumors (Table 2) was not less than that of the patients with nonhormonal tumors,

Number	Reference	Patient Identity	Sex	Age	Habitus	Obesity	Moon Face	Plethora	Striae	Bruisability	Acne	Hirsutism	Voice	Menses	Libido	Phallus or Clitoris	Testes	Breasts	Mental Status	Edema	Blood Pressure	Bone Age	Osteoporosis	Pain	Mass	Miscellaneous Symptoms
TABLE III-A: CUSHING'S SYNDROME (Continued)																										
67	Soffer 1944	Case 1	F	37		+	+	+	+			+		-							+		+			Decreased vision
TABLE III-B: MIXED CUSHING'S SYNDROME																										
1	Walters 1934		F	9		+			+		+	+	Deep	+		+		+			+					
2	Kolodny 1934		F	37		+		+				+	Coarse	-	-	+		-			+				+	
3	White 1936		F	37		+			+		+	+	Deep	-		+					+				+	Chills; fever
4	Walters 1938	Case 4	F	33			+					+		-		Sl. +					+				+	
5	Gross 1940	Case 2 CS	F	3	Male	N					+	+	Deep			+		N			+	9				
6	Mintz 1941	Case 1	F	19		+	+				+	+	Deep	-		+		N			N					
7	Ravid 1942	HC	F	13		+			+		+	+		-		+			P.O. psychosis		+			+	+	Weakness
8	Cahill 1942	Case 11 LF	F	36				+	+		+	+		-		+				+	+				+	Headaches; weakness
9	Neff 1942		F	16 mo		Sl. +					+	+				+					+	72				
10	Kepler 1948		F	26		+	+		+			+				N				+	+					Weakness
11	Walters 1949	Case 5	M	15 mo		+				-	+	+				+					N	N				
12	Walters 1949	Case 6	F	42		+ Then -				?+		+	Coarse	-							+				+	Weakness
13	CPC Mass.Gen'l Hosp. 1949	35481	M	6	Rapid Growth	+					N	+	N			+	+				+		7	N		
14	Quinby 1933		M	12	Well dev. musculature						+	+	Deep			+			Alert		+					
15	Van der Bogert 1933		F	2	Masculine							+				+			Alert		+				+	
16	Wright 1935		F	24		+		+	+			+		-		+					+		+	+		Dyspnea
17	Bruins Slot 1936		F	49		-		+	N		+	+	Husky	-		N					+					? Cardiac decompensation
18	Simpson 1936	RL	F	34	Kyphosis	+		+	+	N	+	+	N	-		Sl. +					+					Polydipsia; headache
19	Broster 1938	Case 45	M	6		+		+	+			+			+	+			Status epilepticus							
20	Reinhertz 1938		F	20		-	+	+	+	+	+	+		-		+				+	+		+	+		Alopecia
21	CPC Mt. Sinai Hosp., 1939	435550	F	30		+		+	+	+		+		-		+			Neurological changes	+	+		+			Weakness
22	Kooyman 1940		M	29		+			+			N	Thin		-	-	-	+	Psycholabile		+		+		+	Weakness; tremor
23	CPC Mass.Gen'l Hosp., 1940	26261	F	56				+	N		+	+				Sl. +				+	+		N to +	+		Dyspnea
24	Ducuing 1940-1941	TC	F	16	Masculine,	N	+	+	+			+	Deep		-	+			N	N	N			+		
25	Weinberg 1941	Case 2	F	30		+			+	+		+		-		+					+		+	+		Weakness
26	Cahill 1942	Case 13 LG	F	27		+		+	+			+		-		+			Very depressed		+		N			
27	Luft	Case 26	M	12		+	+				+	+				+	N		Coma		+		N		+	

Number	RBC or Hgb	Glucose Response	Androgens	Estrogens	Others	Surgery or Autopsy	Supportive Measures	Type of tumor	Atrophy of opposite adrenal	Metastases	Operative Survival	Comments
TABLE III-A: CUSHING'S SYNDROME (Continued)												
67	N	+				S		Lt. Adr. Tumor			?	Outcome?
TABLE III-B: MIXED CUSHING'S SYNDROME												
1	N	N				S	Cortin, saline	Lt. Adr. Aden.	+		+	Recovered. Symptoms disappeared postop.
2	-					S	Blood	Adr. Rest Ca.		+	+	Died 7 mos. postop. with metastasis
3	-					S		Lt. Adr. Ca.		+	+	Inoperable. Rapid downhill course. Died 3 to 4 mos. postop.
4		N				S	Saline, sodium citrate, cortin	Lt. Adr. Ca.		+	+	Lived postop., but symptoms recurred with metastasis
5	N	+	240 to 1120 IU	10120 to 540 IU		S		Rt. Adr. Ca.			+	No postop. insufficiency. Well 8 mos. later
6	+					S		Lt. Adr. Ca.			+	Began to menstruate 3 mos. p.o.
7	-	N		N		S	Saline, oxygen, glucose	Rt. Adr. Ca.		+	+	Stormy postop. course; received x-ray. Died 18 mos. postop. with metastasis. Had developed diabetes
8	+	+		8 RU		S	P.o.: saline and blood	Rt. Adr. Ca.		+	+	Developed adrenal insufficiency 24 hrs. postop., but recovered. Died about 8 mos. later with metastasis
9	+	N				S	Precp.: low potassium diet. Postop.: cortin	Lt. Adr. Tumor			+	Well 9 mos. postop. Authors considered this tumor medullary
10			136 mgm 17-KS	9,400 RU		S	DCA, cortin	Lt. Adr. Ca.		+	+	Recurrence 6 mos. postop. Pt. died 15 mos. postop. Metabolic study performed
11	N		4.1 mgm 17-KS			S	Saline, sodium citrate, cortin	Lt. Adr. Ca.		-	+	"Mixed picture." Alive at least 7 yrs. postop.
12	N	+	3.2 mgm 17-KS	30 RU		S	Saline, sodium citrate, cortin, potassium	Rt. Adr. Ca.		+	+	"Mixed picture." Probable recurrence 7 mos. postop.
13	N		6.6 mgm 17-KS		0.2 mgm 11-oxy.	S		Rt. Adr. Ca.			+	Eosinophiles, 112 cells per cc. Sweat contained less chloride and more potassium than normal
14	N	+				S		Rt. Adr. Ca.		+	-	Tumor mobilized but unable to remove. Died 12 hrs. postop.
15	-	+				S		Rt. Adr. Ca.	N		-	Died 36 hrs. postop.
16	N					S		Rt. Adr. Ca.			-	Died 24 hrs. postop.
17	+	+	2200 IU	100 IU		S		Lt. Adren. Aden.			-	Died 12 hrs. postop.
18	+	+	400 CU	600 IU per liter		S		Malig. Adr. Tumor	Sl. +	+	-	Died few hrs. postop. in shock
19	N		5 IU			S		Rt. Adr. Ca.	+		-	Died 17 hrs. postop.
20	N	+				S		Lt. Adr. Ca.	M	+	-	Died with paralysis and pulmonary edema 23 hrs. postop.
21	N	+				S		Lt. Adr. Aden.	+		-	Died 3 weeks postop. with bronchopneumonia
22	N	N				S		Rt. Adr. Aden.	N	+	-	Tumor not fully removed due to hemorrhage. Died 1 day postop. No distant metastasis
23	N	+	70 mgm 17-KS			S		Lt. Adr. Ca.	+	+	-	Tumor incompletely removed. Died a few days postop. from pulmonary embolus
24	N	N				S	None	Rt. Adr. Ca.	+ Absent	+	-	Tumor not fully removed; died 5 days postop. with tachycardia and hyperthermia
25						S	Postop.: cortin plus usual measures	Lt. Adr. Aden.	+		-	Postop. shock; then gradual downhill. Died three wks. postop.
26	+	+	N	N		S	Postop.: saline, cortin	Lt. Adr. Aden.	+		-	P.o. adrenal insufficiency. Died 23 hrs. postop.
27	-	+	131, 151 mgm 17-KS	20 IU		S	Cortin	Lt. Adr. Ca.			-	Died 2 days postop. *(Also reported by Mellgren, Case 9)

Number	Reference	Patient Identity	Sex	Age	Habitus	Obesity	Moon Face	Plethora	Striae	Bruisability	Acne	Hirsutism	Voice	Menses	Libido	Phallus or Clitoris	Testes	Breasts	Mental Status	Edema	Blood Pressure	Bone Age	Osteoporosis	Pain	Mass	Miscellaneous Symptoms
TABLE III-B: MIXED CUSHING'S SYNDROME (Continued)																										
28	Weisse 1947		F	20 mo		+	+	+				+	Deep			+			Irritable		+					Polyphagia; fatigue; weakness
29	Bartsokas 1947	MZ	F	2	Well dev. musculature	+						+	Deep	+		+		+	Increased intelligence		+	+			+	Polyuria; polydipsia
30	Hain 1947		F	3½		N			N		+	+	Deep			+		N			+	8	N			
31	Cahill 1949	Case 3 CA	F	7		N		+	N		+	+	Deep			+		N			+					Polyphagia
32	Heinbecker 1944	Case 5	F	32 mo		+		+			+	+	Deep			+					+					Polydipsia; polyphagia
33	Raices 1945	Case 18 AC	F	55								+		-		+					+					
34	Talbot 1947	Case 43	M	35		+			+		+	+			N			+			N		N			
35	Moltchanoff 1930		F	6	Long body	+						+		N		+									+	
36	Hunter 1931	Miss B	F	30		+	+	+			+	+	Husky	-		+		N		+	+		+	+	+	Weakness; dyspnea
37	Calder 1935	RM	F	34	Dec. stature	+	+	+			+	+		-		+				?+	+		+			Weakness
38	Gerstel 1935	Case 1	F	30	Well dev. musculature		+	+			+	+		-					Psychotic	+	N					
39	Bottin 1936		F	26		+					+	+		-		+		N			+				+	Hemoptysis; pulmonary metastasis by x-ray
40	Little 1936		F	7½	Male	+	+				+	+	Deep			+			Convulsions		+				+	Headaches; weakness
41	Oppenheimer 1937	Case 1 SF	F	35		+		+	N	+		+		-		+		N		+	+					Hocthidrosis; dyspnea; weakness
42	Fraser 1941		F	56				+			+	+									+		+	+		weakness; dyspnea; baldness
43	Weinberg 1941	Case 3	F	37		+		+	+	+	+	+	Deep Masculine	-		+				+	+					
44	Mintz 1941	Case 2	F	37		+	+	+	+	+	+	+	Deep	-	-	+					+		+			Weakness
45	Clement 1942		F	4½	Increased growth			+				+							Comatose (meningeal hemorrhage)		+			+		
46	Anderson 1943		F	25		+						+		-							Sl. +				+	
47	Cervino 1947	A de C	F	27	Cushing	+	+	+	+			+		±	N	+		+		+	+		+			Weakness; diarrhea; incressed appetite
48	Crooke 1947		F	38		+		+	+	+	+	+		-					Disoriented		+					
49	Pickert 1948		F	22		+	+	+	+			+	Deep	-		+		-	Depressed	+	+		+			malaise; dyspnea; tiredness; fever
50	Vines 1937		F	51		+						+	Deep	-							+					Headache; baldness; failing vision
TABLE IV: ESTROGENIC TUMORS																										
1	Walters 1938	Case 7	F	23 mo	Muscularly developed									+		+					N					
2	Armstrong 1948		M	40		N						N				N	-	+			N			+	+	Night sweats
3	Scott 1948		M	43		N						N			-		-	+								
4	Roholm 1942		M	44		-						N	N		-	-	-	+	N						+	Pulmonary metastasis

Number	RBC or Hgb	Glucose Response	Androgens	Estrogens	Others	Surgery or Autopsy	Supportive Measures	Type of tumor	Atrophy of opposite adrenal	Metastases	Operative Survival	Comments
TABLE III-B: MIXED CUSHING'S SYNDROME (Continued)												
28	N	+	165 CU 120 mgm 17-KS			S	P.O.: saline, cortin	Lt. Adr. Aden.	N		-	Died 3 days postop. in shock. Given large doses of estrogens without effect postop.
29	-					S		Lt. Adr. Aden.			-	Had diabetes insipidus. Patient died 6 hrs. postop.
30	+		5.9 mgm 17-KS	N	Pregnanediol 9 mgm	S		Rt. Adr. Ca.		+	-	Laparotomy only; pt. died few days postop. of peritonitis
31	+	+	76.8 mgm 17-KS			S		Rt. Adr. Ca.		+	-	Unable to remove tumor completely. Pt. died 10 days postop. in coma
32		N				S		Rt. Adr. Tumor			?	"Cushing's syndrome with virilism." Outcome?
33		+	6 to 12 mgm 17-KS			S		Lt. Adr. Tumor			?	Insulin resistant diabetes. Outcome?
34			N		1.3 mg 11-oxy-	S		Adr. Tumor			?	Outcome?
35		+				A		Rt. Adr. Ca.	+	+		Died from tuberculosis and cardiac failure
36	+	+				*		Rt. Adr. Ca.		+		Still living when reported * Biopsy of vaginal wall metastasis
37	N	+				A		Lt. Adr. Aden.	+			Died without operation
38	N	+				A		Lt. Adr. Ca.	N	+		Died from tuberculosis
39		+				A		Rt. Adr. Ca.		+		Received x-ray therapy
40	-	+			AZ neg.	A		Lt. Adr. Ca.	+	+		Died from pneumonia
41	-	+	13,000 MU per liter			A		Rt. Adr. Ca.	+	+		Died from erysipelas. "Typical clinical picture of Cushing's." Normal anterior pituitary
42		+	74 mgm 17-KS			A		Adr. Ca.				
43						A		Rt. Adr. Ca.	+	+		Died in cardiac failure
44	N					A		Rt. Adr. Ca.		+		"Inoperable"
45						A		Rt. Adr. Ca.				Died from a stroke
46	N	N	215 mgm 17-KS		Pregnane- + diol	A		Lt. Adr. Ca.	+			Had massive pulmonary embolus
47	N	+	110 to 175 mgm 17-KS	2800 to 1350 IU	FSH -5	A		Rt. Adr. Ca.	+	+		Cause of death not stated; local infiltration of tumor only metastasis
48	-					A		Rt. Adr. Ca.		+		Cushing's picture disappeared spontaneously after 2 yrs. Only hirsutism and amenorrhea recurred
49	-					A		Lt. Adr. Ca.	+	-		Died of tuberculosis
50						A		Rt. Adr. Ca.			+	Had cyst in pituitary body. Some dispute on classification of this case
TABLE IV: ESTROGENIC TUMORS												
1						S	Saline, sodium citrate, cortical hormone	Encapsulated Lt. Adr. Tumor			+	Menses disappeared p.o.
2	-		34, 180 mgm 17-KS			S		Lt. Adr. Ca.	N	+	+	Tumor not removed. Pt. died 11 mos. p.o.
3			196 mgm* 17-KS	6.3 gamma for 24 hrs. (636 I.U.)		S		Adr. Ca.		+	?	Died, how long p.o. not stated * 70 mgm dehydroisoandrosterone
4			160, 350 IU	2000 MU	Friedman neg. FSH neg.	A		Lt. Adr. Ca.		+		

Number	Reference	Patient Identity	Sex	Age	Habitus	Obesity	Moon Face	Plethora	Striae	Bruisability	Acne	Hirsutism	Voice	Menses	Libido	Phallus or Clitoris	Testes	Breasts	Mental Status	Edema	Blood Pressure	Bone Age	Osteoporosis	Pain	Mass	Miscellaneous Symptoms
TABLE V: MIXED ESTROGENIC AND ANDROGENIC TUMORS																										
1	Holl 1930	Case 1	M	15	Feminine	-					-					N		+						+		
2	Holl 1930	Case 2	M	44		+				+	-				-	-	-	+								Weakness
3	Simpson 1938	XYC	M	35		+ to -									-	-		+			N				+	Peptic Ulcer
4	Wilkins 1948	Case 1 DG	M	4½							N					N	N	+				10				
5	Pico Estrada 1940	Case 1	M	30		N					N						-	+								
6	Pico Estrada 1940	Case 2 M	M	41		N					?-							+								
TABLE VI: TUMORS ASSOCIATED WITH HYPOGLYCEMIA																										
1	Staffieri 1949		M	25														+							+	Goiter; hepatomegaly; splenomegaly
2	Anderson 1930		M	33				•								N			Coma		N					Visual disturbances
TABLE VII: CHORIONIC GONADOTROPHIN — SECRETING TUMORS																										
1	McFadzean 1946		M	29		N					-				-	N	N	+			N				+	
2	Chambers 1949		M	39														+							+	
TABLE VIII: UNCLASSIFIED TUMORS																										
1	Frank 1937	Case 4																								
2	Walters 1938	Case 1	F	33										-										+		
3	Callow 1944	Case 3	F	26							+			-												
4	Warren 1945	Case 79	F	49																						
5	Johnson 1947	Case 3 HW	M	43		-															N		N	+	+	Weakness; anorexia
6	Phillips 1947		F	29				+																+	+	
7	Burke 1934	Case 2	F	65																					+	
8	McGavack 1940	Case 2 CB	F	29		-					+			-		N					-				+	Weakness; pigmentation
9	Warren 1945	Case 66	F	54				+			+														+	
10	Warren 1945	Case 75	F	42		+					+															Hair falling out
11	Hyman 1938	Case 8 VD	F	30		-					+							-						+		Weakness
12	Warren 1945	Case 99	F	40		+					+															Abdominal Swelling
13	Walters 1949	Case 9	F	32																						
14	Tuta 1941	Case 1	F	54		-	+				+			-											+	
15	Cseh 1943		F	6	Tall						+			+											+	Received x-ray to left eye for glioma
16	Mellgren 1945	Case 16	F	42																						

Number	RBC or Hgb	Glucose Response	Androgens	Estrogens	Others	Surgery or Autopsy	Supportive Measures	Type of tumor	Atrophy of opposite adrenal	Metastases	Operative Survival	Comments
TABLE V: MIXED ESTROGENIC AND ANDROGENIC TUMORS												
1						S		Rt. Adr. Ca.		+	+	Tumor inoperable. Pt. died 8 mos. later. Had linea nigra
2						S		Lt. Adr. Ca.		+	+	Later died from recurrence of non-endocrine metastasis
3	N		<100 CU	>400MU		S		Lt. Adr. Ca.		+	+	Recovered. One yr. later developed obesity and plethora. Died two years p.o.
4	N	N'	4.1 mgm 17-KS	5 RU	Pregnanediol neg. FSH neg. 6.5 M U	S		Rt. Adr. Tumor	N		+	Well 4 yrs. later
5						A		Adr. Tumor		+		No lactation from enlarged breasts
6						A		Adr. Tumor		+		No lactation from enlarged breasts
TABLE VI: TUMORS WITH HYPOGLYCEMIA												
1		24 mgm %	24 mgm 17-KS			S	Postop.: DCA, glucose, saline	Rt. Adr. Tumor			+	Hypoglycemic comas, goiter, hepatomegaly, splenomegaly, and gynecomastia disappeared postop.
2	N					A		Lt. Adr. Ca.	+			Died of insulin shock * Slightly cyanotic
TABLE VII: CHORIONIC GONADOTROPHIN — SECRETING TUMORS												
1	N	N			Friedman positive	S		Lt. Adr. Ca.			+	Friedman turned negative p.o. Pt. recovered
2					Friedman positive 50,000 MU	A		Rt. Adr. Ca.		+		"Showed gonadotropic excess but no feminization." Treated with x-ray
TABLE VIII: UNCLASSIFIED TUMORS												
1				+		S		Adr. Ca.			+	"Typical cortical adrenal syndrome." Died 2 mos. postop.
2						S	Saline, sodium citrate, cortin	Rt. Adr. Ca.			+	Menstruated postop.
3						S		Rt. Adr. Aden.			+	Recovered. Left adrenal tumor by perirenal insufflation
4						S		Tumor				No symptoms described postop.
5			86 mgm 17-KS		Pregnanediol 10 mgm	S*		Lt. Adr. Ca.			+	"No masculinization or feminization." Received postop. x-ray. Was moribund 2 mos. later. * Left nephrectomy
6	-					S		Rt. Adr. Ca.			+	Received x-ray postop. Recovered
7						S		Rt. Adr. Ca.	N	+	-	Inoperable. Died 2 days postop.
8	-	N				S		Lt. Adr. Ca.			-	"Some Addisonian disease picture." Inoperable. Died 3 days postop.
9			+			S		Lt. Adr. Ca.			-	Died 9 days postop. Biopsy only
10						S		Rt. Adr. Ca.			-	"Died soon after operation"
11						S		Lt. Adr. Ca.			?	Inoperable. No follow-up
12						S		Ca.			?	(?) partly removed. No follow-up
13			2.4 mgm 17-KS			S	Saline, sodium citrate, cortin	Adenoma			?	"Cushing's syndrome." Outcome?
14	-	+				A		Lt. Adr. Ca.	40x20 x5 mm	+		
15						A		Lt. Adr. Ca.	+	+		Treated with x-ray. Hemorrhage from liver metastasis. Graafian follicles in the ovary
16						A		Adr. Ca.				"Virilism"

Number	Reference	Patient Identity	Sex	Age	Habitus	Obesity	Moon Face	Plethora	Striae	Bruisability	Acne	Hirsutism	Voice	Menses	Libido	Phallus or Clitoris	Testes	Breasts	Mental Status	Edema	Blood Pressure	Bone Age	Osteoporosis	Pain	Mass	Miscellaneous Symptoms
TABLE IX: U.C. HOSPITAL CASES NON-HORMONAL																										
1		EL	F	40		-					N			-				-			N			+	+	Fever; wt. loss; left pleural effusion
2		WJ	M	42		N				N	N				N	N	N							+	+	
3		IHE	M	62		-										N	N				+				N	Shoulder pain; anorexia, cough; dyspnea; weakness; fever; nausea; vomiting
4		BR	F	52		-										N			Mental confusion, stupor		N			+		Spastic left arm and leg; incontinent; enlarged liver
5		FH	M	52		-				N	N					Sl. -	N		N		N			N	+	Abdominal enlargement; wt. loss; venous engorgement of legs
6	Gardiner *	KLM	M	54												N	N				+			+	+	Enlarged abdomen; wt. loss
7		RRS	M	55		-										N	N	N		N	N				+	Epigastric discomfort; anorexia; weakness
8		MNL	F	29	Female	N								N		N				N	N			+	+	Fever
UNCLASSIFIED																										
9		HTD	F	40							+			-				N			N			+	+	Frequency; polyuria; headache; abdominal protuberance; sl. irreg. face pigmentation
MIXED ESTROGENIC AND ANDROGENIC TUMORS																										
10	Lisser 1936	RMB	M	33		-						O to +						+			N			+	+	Hemoptysis
11	Kerr *	GT	M	44	Muscular							N	N		N		N	+			N to +				+	Nausea
12	Kinsell 1949	JCI	F	28	Feminine appearance, heavy musculature					N	N	+	N	N	N	N		Sl. -			N					
13	Reilly	JB	F	2	Masculine appearance, rapid growth						N	+	Deep			+					N	4			+	Fever
14		EF	F	34	Masculine	-						+		-		+		-		N	N				+	Weakness; anorexia; dyspnea
15	Escamilla * 1949		F	63	Tall, thin, masculine	N						+	Husky	-		+					+				+	Enlarged liver; alopecia
16	Hamilton *	Mrs. C	F	44		+						+	Deep	-		+		N			N		M		N	Baldness; fatigability
17	Reilly 1942	AB	M	6½	Very tall	N					+	+	Deep			+	+					15		+	+	Hematuria
18	Lisser 1933	RM	M	5	Strong musculature	N						+	Lowered			+	+		Irritable, embarrassed		N	11			+	
CUSHING'S SYNDROME																										
19		SS	M	52		+				+				+ then -					Poor memory, nervous insomnia	+	+ to N					Weakness; cough; dyspnea; chest pain; ascites; hepatomegaly; splenomegaly
20	Goldberg *	PS	F	12	"Cushing" appearance	+		+			+	+	Deep			N		-	Personality change		+ to N	15				Weakness; dizziness; tremulousness
21	Goldberg *	EZ	F	39	Short, plump	Sl. +	+	+	N	+	+	+		-		N		N	Nervous	+	+		+	N	N	Avidity for proteins; headaches; prominent eyes; mod. weakness; polyphagia; chest pain
22		EA	M	41		+		+	+										Drowsy spells	+	+					
23	Goldberg *	RM	M	32	"Buffalo"	+	+	+	+	+	N	N	N		-	N	N	N	Normal	+	+		+	N	N	Weakness; avidity for proteins

*Described in Part I of this report

Number	RBC or Hgb	Glucose Response	Androgens	Estrogens	Others	Surgery or Autopsy	Supportive Measures	Type of tumor	Atrophy of opposite adrenal	Metastases	Operative Survival	Comments
TABLE IX: U.C. HOSPITAL CASES NON-HORMONAL												
1	-					S	Preop.: blood Postop.: blood, glucose, saline	Bilat. Adr. Ca.		+	-	Died in shock 2 days after left adrenalectomy and nephrectomy
2	N					S	Postop.: glucose, blood	Rt. Adr. Ca.			-	Hemorrhage during operation. Died in shock 10 hrs. postop.
3	-	N				A		Rt. Adr. Ca.	N	+		Died from myocardial infarction
4	-					A		Rt. Adr. Ca.		+		
5	N					S	Postop.: blood, glucose, saline caffein, ephedrine	Lt. Adr. Ca.	N	-	-	Died 2 days postop. with retroperitoneal hemorrhage. Left kidney also removed
6	N					S	Large amounts of blood during operation. Postop.: dextrose, saline	Rt. Adr. Aden.			+	Huge abdominal enlargement simulating cirrhosis
7	-					S	Ephedrine, blood during operation. Postop.: adrenal extract (13 cc.), blood, glucose, saline	Lt. Adr. Aden.			+	Retroperitoneal tumor was biopsied in 1947
8	-					S	Blood, plasma during operation. Blood, glucose, saline postop.	Lt. Adr. Rest Aden.		N	+	Well 2 yrs. later
UNCLASSIFIED												
9	N					S	No adrenal therapy.	Lt. Adr. Ca.		+	+	Peritoneal extension. No adrenal crisis postop.
MIXED ESTROGENIC AND ANDROGENIC TUMORS												
10						A		Lt. Adr. Ca.		+		Had lactation
11	- to +		224.5 mgm 17-KS			A		Rt. Adr. Ca.	N	+		Tumor inoperable; x-ray therapy given. Pt. gained weight next 5 years despite increasing metastases
12	N	N	82.1, 62.2 mgm 17-KS			S	Preop.: 30 units whole extract. At operation 50 cc. whole extract. Postop.: 90 cc. whole extract + saline, glucose	Lt. Adr. Ca.			+	Well 3 yrs. later. 17-KS now normal. Also was given x-ray left adrenal postop.
13	N		+			S	Nothing preop. Postop.: glucose, Ringer's, blood	Lt. Adr. Ca.			+	Given postop. x-ray. Well 14 yrs. later
14	-	N				S	No preop. therapy, Postop.: glucose	Lt. Adr. Ca.		+	+	Died within a yr. with metastasis
15		+	456, 651 mgm 17-KS			S	Preop.: glucose, lipo-adrenal, Ringer's	Rt. Adr. Aden.	+		+	Well 2 mos. later. Beard growth slowing
16	-	+	59 mgm 17-KS			S	Preop.: 10 mgm. DCA, 15 cc. cortin. Postop.: 40 cc. cortin	Rt. Adr. Aden.			+	Diabetes not altered by disease or operation. 17-KS 9.7 mgm 10 days postop. Well 2 yrs. later
17	N	+	29 IU	-		S	Postop.: DCA, eschatin, blood, saline, glucose	Rt. Adr. Aden.			+	Entered in shock. Recovered with adrenal extract. Well 4 yrs. postop.
18	N					S		Lt. Adr. Ca.			+	Well 18 yrs. later. No postop. adrenal insufficiency
CUSHING'S SYNDROME												
19	-	+				A		Lt. Adr. Ca.	N	+		Had x-ray treatment. Rapid downhill course. Died of circulatory failure
20	N	N	14.7 mgm 17-KS			S	Preop.: No adrenal therapy. Postop.: Glucose, saline, 1 cc. eschatin q 4 hr.	Lt. Adr. Ca.			+	Well 8 yrs. later
21	N	+	92.5, 62.4 mgm 17-KS		Kosino-penic neg. 11-oxy. 592 mgm		Cortical extract: 55 cc. before, 65 cc. during, 115 cc. after surgery. Glucose, oxygen, saline, blood, digitalis, p.o.	Lt. Adr. Ca.	+	N	-	Pleura inadvertently punctured at operation. Died 5 days postop. Minute ca. of thyroid
22	+					A		Rt. Adr. Aden.				Died in acute pulmonary edema
23	+	+	13.6 mgm 17-KS			S	Pre-op: testosterone, DCA, Lipo-adrenal, K. During operation: blood, saline, cortin. Postop: cortin, blood, saline	Rt. Adr. Ca.	+	N	-	Infarction of left adrenal postop.

but was actually more than double (30 per cent of the 53 cases where survival was mentioned). Such a high mortality is the more surprising since hormonal tumors are usually smaller and, therefore, technically more easily removed than nonhormonal tumors.

Androgenic influence also proved of no benefit in protecting patients with the "mixed" Cushing's syndrome, as shown by a 59 per cent mortality in 32 cases compared with a 53 per cent mortality in cases of "pure" Cushing's syndrome. While certain reservation must be made in these cases, since the androgenic manifestation might be the result of altered end-organ susceptibility rather than the result of increased secretion of androgenic hormone, it is nonetheless apparent that the androgenic component did not protect the patient from or lessen the hazards of operation. These data do not necessarily mean, however, that the administration of testosterone compounds to persons with obviously increased rate of protein catabolism is contraindicated.

THE possibility that postoperative adrenocortical insufficiency was prevented either by presence of secreting metastases or by a functioning contralateral adrenal seemed the next most important factor to evaluate. Secreting metastases could not be demonstrated to be a factor in immediate operative survival. As a matter of fact, of patients with hormonally-active tumors, the lowest percentage of metastases occurred in those with androgenic tumors, the group in which the immediate survival was the greatest. In Cushing's syndrome (both "pure" and "mixed"), metastases occurred equally among survivors and nonsurvivors. The question must be raised as to whether metastases exercise any hormonal function. Metastases or recurrences usually, but not always, follow the same hormonal pattern as the original tumor. A few unusual cases have been reported, in which hormonal tumors recurred as nonhormonal types or where hormonal tumors recurred with different hormonal function.

As for the factors pertaining to operative survival of patients with adrenocortical tumors of the Cushing's type, no single item could be specifically singled out and documented by this study. Since adrenocortical function is indispensable to life, the most important consideration, on theoretical grounds, is continued maintenance of that function, whether from tissue left behind at the time of operation, metastases, or from continued function of the opposite adrenal cortex. Generous administration of adrenocortical substitution therapy serves this purpose for a short time, but in the long run, if not gradually tapered off, may contribute to the failure of the remaining adrenal tissue to resume adequate function.

In our study, atrophy of the contralateral adrenal, which theoretically should reduce the likelihood of operative survival, could not be demonstrated to be a salient factor in the individual case. It is true that the incidence of contralateral atrophy increases as one passes from nonhormonal tumors (associated with low operative mortality), through androgenic tumors (higher mortality), to tumors with Cushing's syndrome (where the mortality is greatest). In the individual case, however, analysis shows a fairly even distribution of atrophy in survivors and nonsurvivors.

Data relating survival to atrophy are necessarily meager since the functional status of the opposite adrenal is not often known unless the patient has succumbed. There are, however, a few cases reported, namely those of Cahill and of Walters, in which the remaining adrenal was found to be atrophic, but where the immediate postoperative hazards were surmounted by administration of large doses of adrenocortical extract. We are unable to evaluate the possibility of suppression of adrenal function without anatomic change. The mere size of an endocrine organ does not always provide the answer as to its functional capacity.

Localization of the tumor is of paramount interest to the surgeon. It is more efficient to remove a known adrenal tumor through an incision planned for that purpose than to make a transverse or bilateral incision to expose both adrenals simultaneously, at the expense of operating time and accessibility. Injury to the remaining adrenal may also result from unnecessary manipulation. Reilly, Lisser and Hinman[12] have previously stressed the desirability of preoperative localization whenever possible. It has been noted already that tumors occur on either side at random. Operative survival in Cushing's syndrome was not affected by the site of the tumor; operations on the left side resulted in 10 survivals and 10 deaths, and operations on the right resulted in 7 survivals and 7 deaths.

Specific adrenocortical therapy before, during and after operation is a factor more difficult to assess. This, in part, stems from the paucity of cases in which use of adrenocortical extract was mentioned. The actual amounts administered for adrenal replacement were reported in even fewer cases. For the purposes of this paper, it was only possible to note that cortical extract or desoxycorticosterone acetate was given or was not given, along with such other details as the author may have included. In the period which this survey covers, ACTH and cortisone were not generally available. It is interesting that Cahill in 1942[1] speculated that ACTH might reverse the specific deficiencies which cause the patient's death. Since adrenal therapy is intended to be substitutional, its effectiveness is of particular concern in those cases where atrophy of the opposite adrenal was men-

tioned. Of 30 patients with Cushing's syndrome where such therapy was reported, only 16 survived the operative procedure. There were 2 cases in which the author noted that no specific adrenocortical therapy was used; one of these patients survived while the other did not.

Duration of the disease was one factor of theoretical importance which did not lend itself to evaluation. It was almost impossible to estimate from the case reports. Youth could not be demonstrated to play a part, nor did sex incidence. Size of the tumor was also a negligible factor, for the lowest mortality was found in the patients in the nonhormonal group in whom the tumors were most frequently large enough to be palpable.

In the course of this study, a number of interesting observations deserve mention, even though they are not related directly to the problem of survival. For example, contrary to some opinion, adrenocortical tumors of all types occur at random and with almost equal frequency on either side. Of 234 cases in which the site was mentioned, 124 tumors were on the left side and 103 on the right side; of the remaining tumors, 3 were bilateral and 4 were in aberrant locations.

Also of importance was the relatively high incidence of atrophy of the remaining adrenal tissue. This was, as expected, most common in Cushing's syndrome, but was also more frequent in the patients with androgenic tumors than has previously been suspected. This suggests the greater need for therapy aimed at stimulation of the adrenal cortex in the preparation and postoperative treatment of all patients with hormonally active tumors.

One striking finding in the patients with androgenic tumors was the occurrence of precocious testicular development as part of the premature puberty evoked by adrenal androgens. This, however, is not particularly surprising, in view of the known spermatogenic property of testosterone,[14,15] but it is nevertheless in distinct disagreement with previous doctrine, which holds that testicular development indicates a source of precocious puberty at a level above that of the adrenal or gonad.[16]

Pain and the presence of a mass appeared to be valuable localizing symptoms, but the authors hold certain reservations regarding this point, having seen several patients whose pain was due to vertebral collapse with radiculitis or to fractured ribs rather than to tumor.

SUMMARY

Surgical mortality in Cushing's syndrome associated with adrenocortical tumor is excessive. To weigh the factors which might play a part, 277 cases of adrenocortical tumors from the literature and the University of California Hospital files were studied. The cases were grouped according to the principal hormonal manifestations: nonhormonal, androgenic, estrogenic, mixed androgenic and estrogenic, Cushing's syndrome (both "pure" and "mixed" with an excessive androgenic component), gonadotrophic, hypoglycemic, and unclassified. It was found that:

1. The surgical mortality in patients with adrenocortical tumors in general was 34 per cent, and of the surviving patients who were followed, 32 per cent later developed recurrence or metastases.

2. When the groups were separated into various hormonal types, it was found that:

(a) The operative mortality for the patients with nonhormonal tumors was about 12 per cent, but of those who survived the operation, approximately 38 per cent subsequently developed recurrence or metastases. (Only 6 per cent of nonhormonal tumors are benign.)

(b) In patients with androgenic tumors, on the other hand, the over-all operative mortality is 30 per cent and the incidence of recurrence or metastases is considerably less (19 per cent).

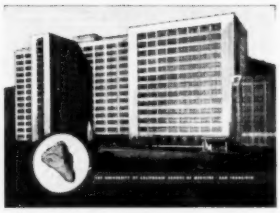
(c) In patients with Cushing's syndrome the presence or absence of a strong androgenic-anabolic component seems to make no difference, as shown by a comparison of the "pure" and "mixed" types of Cushing's syndrome. Only 44 per cent of the patients survived the operation and almost half of those who were followed developed metastases or recurrences.

3. The incidence of contralateral adrenocortical atrophy rose from the nonhormonal group (where it has not been reported), through the androgenic group (29 per cent), to the group with Cushing's syndrome (72 per cent). In individual cases, however, the anatomic state of the opposite adrenal could not be related directly to operative mortality. In cases in which atrophy of the opposite adrenal was mentioned, almost as many patients survived as succumbed. Survivors (with atrophy and without functional metastases) were almost always patients who had received large amounts of substitution therapy.

4. Tumors occurred with equal frequency on both sides, and the operative hazards were not modified by the location of the tumor.

5. Specific adrenocortical therapy was infrequently noted, but when used, it appeared to enhance the chance for survival. Other factors such as age, sex and duration of the disease played no significant role in the surgical outcome.

References cited in this article will be included in the authors' reprints.



THE UNIVERSITY OF CALIFORNIA SCHOOL OF MEDICINE

AT SAN FRANCISCO

The origin of this School of Medicine is coeval with that of the State of California. Shortly after the discovery of gold on the American River in 1848 by Marshall, the wheelwright, and the breaking of the news on the San Francisco waterfront by Brannan, the merchant, California was flooded by intrepid men from all over the world. It is not altogether surprising that within a few months 50 physicians had arrived at the scene of the golden expectancy—so many, in fact, that some of them were forced to take mean jobs in order to live. Some, but not all, for among these physicians were a few outstanding and able men who were not satisfied with the mores of the mining camp and the gaudy and wild ways of San Francisco, and who proceeded to do something about it.

Dr. Elias Cooper started the first medical school in San Francisco in 1859, but it soon languished. Later, he got it going again, and after a long and valiant struggle, it finally became the Medical Department of Stanford University, and now occupies a high place among such institutions.

Of the men who initiated the institution which has become the School of Medicine of the University of California, two were particularly outstanding: Richard Beverly Cole and Hugh Huger Toland. These men were the very antithesis of each other: the one suave, ingratiating, persuasive, agile; the other dour, dominant, stubborn and, at times, vindictive. Circumstances brought about their cooperation, in spite of their thinly veiled hostility to each other—a not uncommon occurrence in public life, where certain opponents who would transfix each other are able to work in harmony in a common cause.

The career of Beverly Cole before he came to California portended the work he was to do here. He was born in Virginia of a cultivated, wealthy father and a demure, young mother whose sole attributes, seemingly, were those of crocheting, smiling and reproducing. When the easy life suddenly came to an end with the father's bankruptcy and death, the hidden talents of the clinging-vine wife were revealed. She opened a boardinghouse, first in the little town and later in Philadelphia, and managed to care for her brood.

Young Beverly left school when he was 16 years old. After a few months as apprentice to a physician in Lexington, Kentucky, he enrolled as a freshman in a small medical school (afterward, the University of Louisville). His aggressive nature soon took him to Philadelphia, where he became a demonstrator in anatomy at Jefferson Medical College. There he came under the influence of Charles D. Meigs, famed in obstetrics, and therefrom sprang his interest in this dramatic field of medicine. On graduation he opened an office and soon had a thriving practice. But the tales coming from California taxed his complacency. He soon abandoned his good start, made arrangements for his family's care, and prepared to go to the new Eldorado. Having no taste for the rough and dirty trip overland, he took passage on a side-wheeler for Aspinwall (now Colón). It was a luxurious boat, but the elegance ceased at the Isthmus. The trip across was hazardous, almost disastrous, for cholera was rampant and men were dying by the dozens. Finally, after arriving in San Francisco, the debonair doctor was shocked to find conditions far from his fastidious liking. Nonetheless, he lost no time in opening an office in a drug

store, and soon he was in the thick of the city's boisterous activities. He became Surgeon to the Vigilante Committee, that lawless but necessary group which redeemed the town from its ruffians and corrupt politicians.

The other leading physician of the time, Hugh Huger Toland, was an austere but able surgeon. In spite of a somewhat forbidding personality, he had developed a large and lucrative practice and acquired the awed respect of many people. Little is known of his relationship with Beverly Cole, except for their polite enmity, until the dramatic shooting of James King of William, editor of *The Bulletin,* by a city supervisor, one James Casey, whose shady past had been exposed by King. Both Cole and Toland were among the seven or eight doctors in attendance. In the confusion, various types of treatment were employed—stimulation, sedation, finger exploration of the tract of the bullet and, finally, a casual sponge thrust into the wound. Infection followed, and King died. Thereupon, the murderer was promptly tried and was hanged by Vigilantes. Later, at the civil trial of one of the accomplices, both Cole and Toland, who were called as witnesses, gave bitterly conflicting testimonies. Toland insisted that King had died not from the assassin's bullet but because of the medical treatment; and he took no pains to conceal his contempt for the opposing witness. Thus began a feud which never ceased, even though both men became active and cooperative on the same faculty.

Toland had been a member of the faculty of Cooper's school. In 1861 he withdrew because of some friction or perhaps because of his ambition, and with his own funds constructed a building, rather impressive for the time, on Chestnut Street. He recruited a medical faculty from Cooper's school, which was temporarily moribund. For a short time all was serene, but ere long Cooper's school came to life again, and the Cooper men withdrew and took the students with them. This left Toland with a big investment on his hands, but no faculty and no students.

The ubiquitous Beverly Cole had returned from Europe at this time with a M.R.C.P. and a variety of other honors, including membership in several exclusive medical societies, and with newspaper notoriety about having been present at soirées attended by royalty. All of this enhanced his local reputation. (Evidence of the real stature of the man is the fact that later he became the first of the four Californians who were chosen to be President of the American Medical Association.)

Cole had not forgiven Toland, nor had he forgotten his antipathy toward Cooper and his nephew, Lane, but he accepted Toland's offer of the Deanship and also the Chair of Diseases of Women and Children. The two erstwhile enemies thereupon joined forces and made overtures to the young University of California in Berkeley, which, still in its swaddling clothes, was under the able direction of Daniel Coit Gilman (later President of Johns Hopkins University). Gilman and the regents were willing to accept Toland's school as a Medical Department, but not on Toland's terms. Toland insisted that his name be attached in perpetuity. Finally the doctor agreed to the transfer on consideration that one of the amphitheaters be called Toland Hall. Dr. Cole also agreed, and a second amphitheater was named for him. And, so designated, they stand to this day.

In 1873, the name of the University of California went up over the door of the school on Chestnut Street. The affiliation was nominal only; the University was having its own financial troubles, and the Medical Department was obliged to get along as best it could on tuition fees and an occasional financial windfall. There is unconscious humor in the "Requirements for Admission" listed in one of the early announcements; obviously few applicants were turned away because of academic shortcomings.

For more than 20 years the teaching was carried on at the Chestnut Street building. As one looks back at the list of graduates of the time and remembers their subsequent attainments in medicine, it is plain that the quality of instruction must have been adequate for the period.

Dr. Cole apparently kept up his political fences, for in 1895 he was actively seeking an appropriation from the State Legislature. Due to his efforts, 250 thousand dollars were voted for the erection of buildings for the Schools of Medicine, Dentistry, Veterinary Medicine, Pharmacy and Law. Since the act made no provision for the location of the new medical campus, there was the usual backing and filling with advocates of one or another site. One group proposed that the buildings be constructed at Black Point near the city's home for inebriates, who would serve as passable teaching material; a second group thought a location close to the new City Hospital on Potrero Avenue was more desirable. But Cole, either with the idea of having the campus on an eminence overlooking the city (including the new Cooper-Lane Building of shiny brick) or with a prophetic vision of the city's

(Above) Present buildings, before construction started on new installations.

(Left) Old building on Chestnut Street.

growth, induced his friend, Adolph Sutro, to donate a tract of land on the north slope of Twin Peaks, those forest-covered hills in the exact geographic center of the present city. It was halfway to the beach; there were no streets nor sidewalks nor transportation, but with characteristic vigor Cole persuaded the supervisors and the Market Street Railway to correct these shortcomings. As a result, whatever the doctor's motives, the School of Medicine has an outstanding campus.

The building proceeded for three years, and in this day of high costs, it is interesting to note that all four buildings were constructed within the appropriation. They were good buildings too, for they withstood the 'quake of 1906 with only minor damage, and all but one are still in use today.

The school was transferred to the new quarters in 1898. This was the turning point in its career. The Berkeley authorities gave increasing financial support, and the administration was able to attract a number of remarkable men. Some were local leaders; others were from eastern schools. The early disputes became a memory, and the school soon caught the stride of medical education in this country and abroad.

The Outpatient Department, which long had been located on Montgomery Street, had well served its purpose. It was transferred to the new location as soon as the growth of the city and improved transportation facilities made it advisable. At about the same time a number of rooms in the Medical Building were converted into wards for teaching-patients. These, together with the wards at the San Francisco City Hospital, used before 1906, provided the teaching needs.

In 1917, a group of friends of the school, headed by the revered Herbert C. Moffitt, built and presented to the University the University of California Hospital as a combined private patient and teaching institution. The Nurses' Home followed. In 1943, the Langley Porter Clinic building was erected by the state and became the headquarters of the Division of Psychiatry. An Animal Surgery pavilion rose, adjoining the Hooper Foundation; a Radiologic Laboratory was erected; and a building for Research in Arthritis and Related Diseases was provided during 1951.

Just before World War II, the State Legislature was asked for funds for a new teaching hospital, as well as for a building for the School of Medicine. Two million dollars were appropriated for a beginning. Then the war intervened, and it was not until 1950 that construction began. Meanwhile the appropriation had been increased to 20 million dollars. At present the two 13-story structures (with provision for two more floors to be added later) are well along in construction and will be ready for occupancy next year. Over-all plans are being made for a 50 million dollar development program on the San Francisco campus. With the probable continuing growth of the state, this goal may well be reached within a few decades at most.

Under the skillful direction of successive Deans (Cole, McLean, D'Ancona, Moffitt, Whipple, Porter, Marriott and Smyth), the school has gone steadily forward. Among its many men and women are earnest physicians who have given of their time and talents. Space limitations will not permit listing of their names, but they include a sizable part of the membership and officers of every scientific medical organization in America, as well as of numerous societies abroad. And through their common efforts, this School of Medicine is proud to be numbered among the world's select.

WILLIAM E. CARTER, M.D.

For general practitioners, as well as specialists, this department offers the latest, proved methods of treatment of conditions encountered in an average practice. It is not, of course, intended to present these discussions as the only acceptable therapeutic procedures to be used, but rather to offer simple regimens and recommendations based on the extensive experience of the physicians who prepared these summaries.

SICKLE CELL ANEMIA

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Among the congenital hemolytic disorders, sickle cell anemia ranks first in its ability to disguise itself with varied cloaks of presenting signs and symptoms. The companion of diagnosis is treatment and, as the former may be difficult, often the latter is even more perplexing. For these two reasons alone, despite other intriguing aspects, this disease presents a challenge to the physician.

The disorder derives its name from the sickle-like appearance which the red cells assume under conditions of reduced oxygen tension or after exposure to reducing agents such as dithionite or BAL (2, 3-dimercaptopropanol). Almost exclusively a disease of the Negro race, approximately 7 per cent of the North American Negroes have sickle cell trait,[1] or red cells which will assume a change in shape from biconcave disks to crescentic or holly-leaf forms under reduced oxygen tension. Clinically they have no symptoms referable to this congenital red cell abnormality. About 1 in 40 persons with "sickle cell trait" suffers from a hemolytic anemia directly related to the distorted shape of the cell. It is in these patients that we make the diagnosis of sickle cell anemia.

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Recent investigations of the genetics of this disease suggest that sickle cell trait is a heterozygous form of inheritance of the sickling characteristic, while sickle cell anemia is homozygous.[2] Pauling[3] and others[4] have shown there exists in sickle cell anemia a type of hemoglobin which is electrophoretically different from normal hemoglobin. For this reason sickle cell anemia has been classified as probably the first of the molecular diseases. The red cells of those with sickle cell trait contain both types of hemoglobin, with the abnormal variety ranging from 24 to 45 per cent.[5]

There is no need for treatment in sickle cell trait (SCT) for patients have no specific symptoms nor does the condition compromise life expectancy. The diagnosis of sickle cell anemia (SCA) is made by finding the misshapen red cells in the presence of anemia, reticulocytosis, usually leukocytosis, hyperbilirubinemia of the indirect type, increased fecal and urine urobilinogen, as well as of a past history of abdominal and joint pain and hemolytic crises. Sickle cells are not found in the circulating blood of the SCT, but can be produced when the blood is placed under the proper conditions of reduced oxygen tension or with the reducing agents previously mentioned. Contrariwise, the

SCA patient has circulating sickle cells which may be found on the counting chamber or in the peripheral smear, a simple finding diagnostic of sickle cell anemia. The symptoms of the disease usually begin after the first six months of life, although there is a case on record in which signs were present at birth and other causes for a hemolytic anemia were excluded.[6]

CLINICAL COURSE

For convenience, the clinical course may be divided into two phases: the latent, or periods of relative freedom from acute symptoms, and the acute, or the episodes of hemolytic and visceral crisis which punctuate the course of this disease. The symptomatology of the latent phase varies considerably. Many patients express no specific complaints other than easy fatigability, slight to moderate dyspnea on exertion, vague pain over the precordium, or fleeting twinges of abdominal pain or arthralgia. Recurring episodes of priapism have been a major complaint in two of our patients. Cholelithiasis, similarly found in congenital hemolytic icterus, incident to the large amounts of bilirubin produced each day, is a frequent complication.[7] Rheumatic fever and rheumatic heart disease are common errors in diagnosis in children during the latent periods of the disease. The diagnostic potentialities in sickle cell anemia exclude no organ or system, so subtly can it mimic other diseases.

During remissions the processes of blood destruction and production are at an equilibrium, which is so regulated as to make most patients moderately anemic, with hemoglobin values ranging between 8 to 9 gm. per 100 ml. However, in a few, the anemia is more severe, ranging in hemoglobin values from 6 to 7 gm. per 100 ml. One of the biochemical measurements of blood destruction, hyperbilirubinemia of the indirect type, may be at a different level, reflecting a different degree of the breakdown of the circulating sickle cells. If factors which control this equilibrium could be correctly ascertained, these data might be important in directing a more successful therapy.

Treatment during the latent phase is generally symptomatic. Aspirin is of value in the mild arthralgias. Little or nothing can be done for the anemia. Liver, iron, folic acid and the host of other hematinics are of no value (unless a specific indication for one of these medications should arise). Some patients, however, express a sense of well being while taking ferrous sulfate in doses of 200 mg. three times a day. When such medication is withheld their complaints increase. For this reason we have permitted some of them to continue to take iron without any demonstrable effect on the anemia or hemolytic process. Both plasma and whole blood transfusions have been tried, the latter without significantly changing the erythrocyte levels. Frequent multiple transfusions accomplish little, although temporary increases in the red cell count and hemoglobin can be obtained. It has been reported that the fecal urobilinogen content may become lower after either whole blood or plasma[8] thus suggesting a decrease in the production of bile pigments, but the contrary has also been seen, in that transfusions appear to have accelerated the formation of bile pigment, presumably through an increased breakdown of the red cells. Transfused normal red cells, and even sickle cell trait cells, will live a normal life span in the sickle cell anemia patient,[9] and even in some manner influence the degree of in vivo sickling,[17] but because of the prohibitive cost, the risk of eventual cross sensitization, and transfusion reactions inciting crisis, we have not used them as methods of treatment in the latent phase of the disease. The patients become relatively adjusted to the chronic anemia, although clinical cardiovascular manifestations are invariably present.

The present treatment for priapism is unpredictable, in that measures which produce gratifying results at one time will fail the next. We have used transfusions, analgesics and bed rest, and others have used agents to promote increased blood flow such as tetraethylammonium chloride, and have suggested the use of caudal block. In many instances the priapism will subside after several hours without treatment.

There is a recent report of a good response in sickle cell anemia following splenectomy[10] but splenectomy is generally contraindicated. The spleen becomes fibrotic and smaller as time elapses, and actually the disease eventually pro-

duces an "autogenous splenectomy." Sufficient evidence has not appeared concerning the use of adrenocorticotropic hormone and it has appeared to promote crisis, so at this time its use, as well as that of its partner, cortisone, seems in need of further study.

COMPLICATIONS

One persistent complication in the natural course of sickle cell anemia is the development of leg ulcers, the pathogenesis of which has been the subject of much controversy. Generally, it is assumed that the ulcers result from localized areas of tissue anoxia incident to the formation of sickle cell "thrombi," or sickle cell stasis in the smaller vessels of the affected area. The degree of anemia, however, does not bear any relationship to the presence or multiplicity of leg ulcers, which are usually on the anterior shin or around the malleoli. Injury to the shin or ankle has been, in our experience, the most common predisposing cause. Secondary infection invariably occurs in the lesion, and the ulcers may reach 3 to 5 cm. in diameter and be 2 to 4 mm. deep.

The most important local factors in the treatment of the ulcer are bed rest, control of infection, the production of healthy granulation tissue and the subsequent grafting. The larger ulcers will not fill in from the sides and skin grafts are necessary. We have felt that transfusion at this time plays an important part in ulcer management, and think it advisable to try to get the hemoglobin values around 10 gm. per 100 ml. during the time in which the ulcer bed is being cleansed and healthy granulations stimulated. For this means, recently Ende[11] has suggested the use of hyaluronidase. Following his method, we have used ALIDASE® diluted 1:1 with saline and placed directly in the ulcer crater at least once or twice daily in an effort to dissolve and loosen the thick heavy necrotic debris covering the base of the ulcer. After several days, granulations begin to make themselves evident. Infection is controlled by both local and systemic antibiotics, and when this is accomplished, grafting is done. Success probably depends upon a number of factors, but active treatment seems advisable for one of the most persistent and worrisome symptoms of the disease. The site from which the graft is taken heals without difficulty.

Pregnancy can probably be considered a complication of the latent phase. With reasonably careful prenatal management, the gravid patient with sickle cell anemia can carry her fetus to term, and therefore it cannot be considered an indication for therapeutic abortion, unless secondary complications of a severe nature arise. Treatment during the prenatal period would not be different from that employed in a usual pregnancy. The relatively increased susceptibility of these patients to infection and the increased infant mortality would suggest advice against future pregnancies in patients with sickle cell anemia.[12] Whole blood transfusion is not of any more necessity during pregnancy than otherwise, and should not be used routinely, but only for specific indications. During delivery it is wise to use local anesthesia, to have whole blood readily available, and to take every precaution against development of infection, blood loss, shock, *and particularly anoxia.*

Another important aspect in the management of the remission is rehabilitation of the patient for gainful employment. All too often these individuals become public wards because of the recurring crises which take them from work and eventually cause them to lose their jobs. The majority of the patients come from a social class where manual labor is the chief employment. It appears that hard physical work may be associated with increased symptoms and possibly increased incidence of crisis. Where a sedentary position is available it is to be preferred. Employment as waiters, checkers, bellhops, messengers, and domestics is to be recommended.

CRISIS OF THE DISEASE

Crisis is the most serious aspect of the disease. More often than not, the first time the patient is seen by a physician he will be in a mild or severe crisis. Again the diagnosis is apt to be mistaken if the possibility of sickle cell anemia is not taken into consideration. For the most part crisis is ushered in over a 12 to 24 hour period with increasing symptomatology of abdominal

pain, nausea, vomiting, fever, aching in the back and limbs, which may be accompanied by chest pain, dyspnea and great restlessness. In children and young adults the abdomen is frequently mistakenly opened as a surgical emergency. Physical signs and roentgenograms of the chest often suggest the diagnosis of either lobar or bronchopneumonia. When such findings are evident, a clue to the true disease process is a rapidly changing roentgenogram and the absence of pathogenic bacteria in the sputum. Enlargement of the liver and increasing jaundice of the direct type indicate that parenchymatous and vascular changes in the liver are frequent accompaniments of the crisis.

All the mechanisms which bring about the change from the latent phase to an acute and dangerous illness are unknown. Systemic infections seem to bear some relationship to the period of crisis, and must always be considered in the management. Vascular stasis, increased blood viscosity and "pseudo"-thrombosis might account for the multiplicity of signs and symptoms which can arise during the crisis. Green and Conley[13] have published their observations which indicate that a true sickle cell crisis may develop in a person who has not been found in a latent phase with the usual manifestations of anemia, reticulocytosis, etc. On the contrary, between acute episodes they are asymptomatic with normal hematologic picture. We have seen a similar patient in our clinic, who in the latent phase presented none of the usual hematologic signs. Critical studies of such instances are necessary for they may be important links in further understanding this disease.*

Hematologically, most crises are attended by an accelerated destruction of the sickle cells and an accompanying intense erythroid hyperactivity of the bone marrow. Theoretically these aspects of the acute phase can for a time sustain themselves by the increasing anemia, thereby decreasing tissue and vascular oxygen tension, with consequent production of a greater number of circulating "sickled" cells, and hence the formation of a vicious circle. Soon the capillary beds are filled with the deformed crescentic red cells.

In spite of the rapid red cell destruction hemoglobinuria does not occur. The hyperactive marrow is reflected in the peripheral circulation by normoblastosis, reticulocytosis and leukocytosis. Often a part of the leukocytosis is a great increase in the number of normoblasts which are counted as white cells in the dilute acetic acid of the counting technic. It should be stressed that reticulocytosis is singularly important in the differential diagnosis of the sickle cell crisis from the acute surgical emergency and other pyogenic infections which it so often simulates, since infection generally inhibits erythropoiesis and reticulocytosis.

The hematologic discussion of crisis is not complete without mentioning a rare type of response recently described by Singer.[14] This has been called the "aplastic" type because of the marrow hypoplasia, reticulocytopenia, low or normal white count and marked anemia. In a patient recently studied in our clinic with this type of response, two 500 ml. whole blood transfusions were given. Within 36 hours she developed a marked change in the blood picture, with a white count reaching 50,000 and a leukemoid picture, reticulocytosis, and a pronounced change in the activity of the marrow. Recovery from the acute stage was satisfactory, and when seen several weeks after leaving the hospital, she was in a typical latent phase of sickle cell anemia with the usual hematologic picture.

MANAGEMENT OF CRISIS

The chief measures for combatting the crisis are directed at the sickling phenomenon, the anemia, shock, vascular stasis, pain and restlessness. Oxygen has long been advocated and is best given by mask when the patient is first seen, then later shifting over to the tent if it is deemed necessary. At times it appears to be of definite benefit as evidenced by subsiding pain and restlessness. Continuous oxygen therapy has its drawbacks for it was demonstrated some years ago by Reinhard and co-workers[15] that after several days of continuous oxygen therapy in the latent phase the bone marrow was depressed, reticulocytopenia developed, and the anemia increased. This response may be deleterious to the

*While this review was in the process of completion, Kaplan, Zuelzer and Neel[28] described a clinical syndrome involving still a third type of abnormal hemoglobin which occurred in combination with either sickle cell hemoglobin or normal hemoglobin. With the former it appeared to modify usual severe manifestations of the disease, excepting those which could be termed crises.

patient, but is quickly reversed when oxygen is discontinued.

Transfusion is necessary where there is increasing or marked anemia and particularly in shock and vascular collapse. But multiple transfusions also have a depressing effect on hematopoiesis in sickle cell anemia.[16] Nevertheless, the fact that they appear to diminish the amount of in vivo sickling[17] adds to the rationale of their use. The danger of transfusion reaction is perhaps increased, but is outweighed by the gravity of the crisis unless the patient is known to be particularly susceptible to transfusion reaction.

Mild sedation and analgesia aid greatly in the management, but too enthusiastic use of morphine or barbiturates is to be carefully avoided. Small doses of the analgesics usually suffice. After these measures have been instituted, the acute attack may gradually subside in a period of 12 to 36 hours. Heparin and DICUMAROL® have been tried for the purposes of preventing thrombotic episodes but their value is yet to be proved.[18] Agents to promote a change in blood viscosity have been used in sickle cell anemia and some effect on viscosity obtained.[19] Where infection is thought to be a precipitating cause specific treatment for this is indicated. Fluid balance should be maintained and an appropriate diet given when the abdominal symptoms lessen.

Perspectives in therapy would seem to converge toward a number of pertinent clinical and laboratory observations. Sickle cell symptoms are particularly rare in infants who eventually develop true sickle cell anemia. There is a relative paucity of sickling in the blood of such infants.[20] The red cells of the fetus and newborn contain a hemoglobin which is different in its physical properties from adult hemoglobin.[21] This fetal hemoglobin disappears within the first six months. The red cells of a person with sickle cell trait will undergo exactly the same changes under reduced oxygen tension or with reducing agents as the cells from a person with sickle cell anemia, but not as easily[22] and in all probability do not sickle in vivo in the SCT. Sickle cells from the anemic patient have a shortened life span when transfused into the normal, but sickle cell trait cells have a normal life span even when transfused into a patient with sickle cell anemia.[9] Thus the destructive phenomena are a function of the ease with which the cell undergoes its change in shape. The hemoglobin in the SCA cell is all of one variety, with perhaps some rare exceptions,[23] while in the SCT cells it is mixed with normal.[5] Concentrated solutions of SCA hemoglobin will form tactoid birefringent alignment,[24] and the sickling characteristic is thought to result from alignment of the hemoglobin molecules with subsequent twisting resulting in the deformity of the cell.[3]

One idea is suggested by the consideration of these data. A variable amount of a different hemoglobin in the presence of SCA hemoglobin will deter the ease with which molecular alignment can occur. Thus if some biochemical means could be stimulated to change a small fraction of the SCA hemoglobin to another molecular form or promote the formation of perhaps a small quantity of normal hemoglobin, one might convert the SCA patients into physiologically SCT patients, and thus control the latent phase, and perhaps the acute phase of the disease. This attack could be on the red cell itself through some environmental agent, or by changing one of the enzyme systems active in the formation of globin in the developing erythrocyte. Also needed is a clearer explanation for the crisis, and it is possible that antigenic hemolytic systems play a part. The findings of Schneider,[25] that one could produce antibodies to sickle cells, are significant. Closer attention should, in the future, be directed toward investigations of antigen-antibody mechanisms in sickle cell disease.

SICKLE cell anemia remains a diagnostic and therapeutic problem. At present no simple solution or answer is available in the many problems of treatment. In diagnosis every Negro patient with protean symptomatology should be regarded with a high degree of clinical suspicion for sickle cell anemia. The proof lies in the finding of the characteristically distorted red cell. And, finally, the disease in all of its aspects, both clinical and investigational, is a challenging problem to the physician. Its solution would bring great benefit to its hundreds of sufferers.

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MANAGEMENT OF ARTERIOSCLEROTIC HEART DISEASE

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Arteriosclerosis in the coronary vessels is arteriosclerotic heart disease. When this process reaches a degree that leads to symptoms, it is not subject to cure or even to significant reduction in amount by treatment. However, proper management can often lessen to an appreciable degree the discomfort and disability that comes from arteriosclerotic heart disease. It is such management that concerns us in this discussion.

Coronary arteriosclerosis may manifest itself as angina pectoris, coronary insufficiency, or coronary occlusion with myocardial infarction, or (subject to some academic dispute) it may be manifested by myocardial inadequacy with or without congestive failure, arrhythmia or anginal pain. In the presence of this degenerative phenomenon, almost any type of cardiac disease manifestation may be present and management of arteriosclerotic heart disease involves all the problems of other heart disease. We can consider only general principles in a paper of this length. Because space is limited and because it entails special problems, we do not discuss the management of the myocardial infarct.

The management of arteriosclerotic heart disease can conveniently be discussed under the headings: psychotherapy, activity, diet, medication, other measures, and periodic observation.

PSYCHOTHERAPY

The patient's attitude and level of emotional

stress are of first importance. Emotional tension puts an added load on the heart and restricts coronary blood flow. Emotional responses are the chief determinants of the patient's actions and of his voluntary responses to his disease. The patient has called the physician because of what appear to him to be relatively grave symptoms. He may be frightened. He may have distorted knowledge of heart disease or distorted ideas of the correct diagnosis. Insofar as his mental endowment permits, the patient should know and understand his diagnosis, its requirements and the prognosis. Explanation should be designed to give him respect for, rather than fear of, his disorder. His emotional stress over his own disabilities can best be controlled in this manner. Other emotional problems may require simple psychotherapy or even a more formal psychiatric approach. Regulation of his activities beyond the physiologic necessities can be of material value in lessening emotional stress. The patient should be treated as a person rather than as "that old man with the arteriosclerotic heart."

The manifestations of arteriosclerotic heart disease (other than arrhythmia) are, in general, due to a demand for greater activity and work by the heart or for greater blood flow through the coronary vessels than is possible under the conditions imposed. Management of the condition consists of two parallel efforts: one, to increase the capabilities of the heart muscle or coronary vessels to the slight degree that this is possible, and the second, but equally or more important effort, to reduce the patient's demands on his heart to its capabilities. The latter is done largely through control of activity. This principle should be understood by both physician and patient. Its understanding will allow a more sane and less frightened approach to one of the manifestations of old age.

ACTIVITY

In every case of heart disease—arteriosclerotic or otherwise—the patient's activities must be held, if possible, to a point below that at which acute symptoms occur. With more severe disease, it is desirable to reduce activity to the minimum, to keep the patient in bed except for use of a bedside commode for bowel movement. It has been shown that this requires no more exertion than does the use of the bedpan. The orthopneic or other bed patient certainly can sit propped against a back rest, or even sit on the side of his bed for a while, with less expenditure of energy than would occur if he were restless in bed.

With less severe disease, where symptoms are not constant, dyspnea, palpitation, or the angina of effort usually will occur on a fairly fixed degree of exertion: after climbing a certain number of steps, after doing a specific job, after walking a certain distance. The patient's activities should rigidly exclude such degrees of activity as are known to produce symptoms. Here it is the rate of work that is most important. An activity may at times be done slowly with none of the symptoms that would occur if it were done rapidly. Where stairs produce dyspnea or angina and limitation of the patient to one floor is impractical, walking up a step at a time—baby-fashion, slowly, with a rest on the landings—will often produce no symptoms. A one story house, a downstairs bedroom (and bath), a first floor apartment, or the installation of a home elevator when the patient can afford it, will lessen the necessity for activity. Similar restriction of activity on the job and away from home is essential for all patients with heart disease of a degree and type that results in an increase in symptoms on effort. In each instance, we are trying to so rearrange the patient's habitual activity that he never puts more load on his heart than it can easily carry.

Ambulatory patients with heart disease should further be made to rest at frequent intervals during the day, with an hour or two on their beds in midday. These older patients usually do not admit diminished stamina, but push on despite fatigue. Prescribed rest periods will counteract this tendency.

When there is reason to believe that the heart's capabilities have increased, activity also may be increased gradually, but it should always be kept at a level well below that which produces symptoms.

DIET

The diet of the patient with arteriosclerotic

(or other) heart disease is moderately important. Digestion and the specific dynamic action of food is said to utilize about 10 per cent of its caloric value and this is expended chiefly in the first hour or two after a meal. For this reason, it is best that the patient eat no particularly large meal and that activity be even more limited immediately after meals. The hour's rest after the midday meal accomplishes this, as well as a desirable break in his day's activity.

The total amount that the patient eats should be such that his nonedematous weight will be reduced to and maintained at 10 or 15 per cent below his theoretic ideal for height, sex and body build. Note that age is not a factor. Excess weight requires proportionate work by the heart and proportionate coronary blood flow. Restricting the patient's activity will tend to increase his weight; his food intake also should be restricted to attain or maintain his desired weight.

It is generally immaterial what the patient eats qualitatively. Any harm properly ascribable to protein is probably outweighed by the greater sense of well-being of the patient on a normal or high protein diet. The possibility of the salt depletion syndrome makes the "salt-free" diet inadvisable for long periods. On the other hand, excessive sodium intake probably will predispose to edema in these patients. A usually satisfactory compromise is to instruct the patient to have his food cooked with normal amounts of salt, but not to eat any particularly salty food and not to add any salt to his food after it is served.

There is no demonstrable rationale in restriction of fluid intake. The patient on a low salt diet will have a greater net loss of fluid if his intake exceeds 3000 cc. daily.

MEDICATION

Medication cannot cure arteriosclerosis nor regenerate myocardium that has degenerated and is now replaced by fibrous tissues. Although it can lessen the severity of the manifestations, medication must not be looked upon as the major element in management of arteriosclerotic heart disease.

Digitalis is of some value when there is myocardial inadequacy or long-standing auricular fibrillation. Its value in angina is probably nil. For routine use, I prefer pills of digitalis leaf given by mouth in only slightly subtoxic doses. True, many cardiologists are using the newer purified glucosides, but in most cases their use in preference to the powdered leaf is not necessary. The digitalis leaf with which we are all familiar is adequately effective. When there is long-standing auricular fibrillation, digitalis is used to control the rate. Here it may be of dramatic effect. Otherwise, its value is more often subject to question.

Quinidine is useful in certain disturbances of rhythm, particularly in the control of extrasystoles and ectopic rhythms. It is less often of value in the fibrillation of arteriosclerotic heart disease. With firmly established fibrillation, as is most common in these cases, digitalis is of greater value. If quinidine produces no diarrhea, it may be given in as large doses as are necessary, within rather wide limits.

Mercurial diuretics are probably the most valuable drugs we have in the treatment of heart failure of arteriosclerotic or any other origin. An effective mercurial should be given whenever there is real or potential failure, injected daily or every second day until the patient's weight no longer decreases; then less and less often, to the point where the least possible amount is given with no increase in weight. Effective preparations for oral use also are available. There is probably no harm in the long-continued use of these diuretics; other diuretics, however, are not as useful as the mercurials. Subclinical failure—fluid retention without clinical edema—is not uncommon and mercurial diuretics here will materially improve the patient's well-being and the disadvantage against which the heart must work. Diuretics should be tried whenever there are symptoms of myocardial inadequacy, even though there is no clinical evidence of failure. Their use then will be regulated by the patient's subjective benefit.

Aminophylline tends to increase coronary blood flow. A 7½ gr. aminophylline suppository at bedtime often will lessen the nocturnal dyspnea these people may have. It is of less value in other dosage forms.

The nitrites will increase coronary blood

flow. Nitroglycerin is the most convenient of these to use and should be taken to relieve anginal pain. Amyl nitrite and sodium nitrite are probably equally effective but nitroglycerin is certainly the easiest to use.

The longer-acting nitrites, to be taken three or four times daily, have at least some theoretic value. I prescribe them whenever there are symptoms of coronary inadequacy. The preparation I use also contains ¼ gr. of phenobarbital and it is questionable which drug produces the apparent effect of lessening the frequency of angina.

Sedatives are very valuable. They lessen the violence of emotional response and lessen the frequency of angina by reducing the sensitivity of the emotional trigger. Sedatives lessen restlessness and, therefore, work output. Phenobarbital in ¼ gr. doses three or four times daily is the usual prescription. With larger or more frequent doses, undesirable cumulation is more likely. Three to five grains of chloral hydrate, in solution, given by mouth two to four times daily is often of greater value to the arteriosclerotic patient than are the barbiturates. The value of the regular and continuous use of these drugs outweighs the danger of possible habituation in a patient in this age group.

OTHER MEASURES

The patient with coronary arteriosclerosis should use no tobacco; in any form, it narrows the coronary vessels. "Cutting down" on the number of cigarettes rarely is possible. It is best for the patient simply to stop smoking.

Alcohol is a particularly salubrious sedative when taken in moderation. However, in prescribing alcohol the physician must be very cautious to avoid conflict with the patient's or the family's ideals and he must not, by his prescription, give license to the psychopathic alcoholic. A moderate highball or cocktail before the evening meal, or possibly more often, is of very great value when these contraindications do not conflict.

PERIODIC OBSERVATION

The patient with arteriosclerotic heart disease should be seen by his physician at regular intervals to discuss the many problems that may seem petty to the physician but which loom large in the minds of the patient and his family. Frequent observation is of psychotherapeutic value. Too, it tends to keep the patient on appropriate medication. It allows a check on the size of the liver, the amount of edema and the patient's weight.

It has not been intended to stereotype this treatment. Arteriosclerosis of the coronary vessels varies widely in its manifestations from patient to patient. Its management must vary as widely according to certain basic principles.

MEETINGS AND POSTGRADUATE COURSES

University of Colorado School of Medicine, Denver

For further information on the courses listed below, write to Postgraduate Education, University of Colorado School of Medicine, 4200 East Ninth Avenue, Denver, Colorado.

Poliomyelitis, May 1-3, presenting a review of the diagnosis and management of patients.

Traumatic and emergency surgery, May 19-20, for both general practitioners and specialists.

Psychiatry for general practitioners, June 26-28, with emphasis on psychotherapy. Guest lecturer will be Dr. William T. Shanahan, Galveston.

American College of Physicians

The courses listed below have been arranged through the cooperation of the directors and the institutions at which they will be given. For further information and for registration, write Dr. E. R. Loveland, Executive Secretary, 4200 Pine Street, Philadelphia 4, Pennsylvania.

Electrocardiography: Basic principles and interpretation, May 12-17, at Massachusetts General Hospital, Boston; Conger Williams, M.D., director.

Trends and newer developments in internal medicine, May 12-16, at Hahnemann Medical College and Hospital, Philadelphia; Charles L. Brown, M.D., director.

Physiological basis for internal medicine, June 2-6, at University of Toronto Faculty of Medicine, Toronto; Ray F. Farquharson, M.D., director.

University of Minnesota Medical School, Minneapolis

Continuation course in eye, ear, nose and throat, May 12-14, at the Center for Continuation Study. Course is intended for general practitioners.

Course in allergy and hematology, May 15-17, at the Center for Continuation Study, intended primarily for general practitioners. Dr. Will Cook Spain will be the visiting faculty member, and the course is under the direction of Dr. C. J. Watson.

American College of Chest Physicians, Chicago

Eighteenth annual meeting at the Congress Hotel, Chicago, Illinois, June 5-8. The Board of Examiners of the College announces that the next oral and written examinations for Fellowship will be held in Chicago on June 5. Candidates who wish to take the examinations should contact the Executive Secretary, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

POSTGRADUATE MEDICINE

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EDITORIALS

APRIL 1952

INTERNATIONAL HEALTH PROGRAMS

In his State of the Union message early in January, President Truman in discussing the Point Four program stated, ". . . there is nothing of greater importance in our foreign policy. There is nothing that shows more clearly what we stand for, and what we want to achieve."

This statement is particularly true in the field of international health, not only for the Point Four program under the Technical Cooperation Administration, but in our bilateral health activities under the Economic Cooperation Administration and the Institute of Inter-American Affairs and in our participation in the World Health Organization as well.

Last year the United States spent approximately $40 million on these programs. We did this for two reasons: first, to protect ourselves against the incursion of disease from abroad; and second, to remove the barrier against economic development which massive ill-health interposes in many areas of the world. Both our bilateral and multilateral international health programs are premised on recognition of the fact that sick men cannot be happy or productive.

The opportunities for strengthening the free world through health activities are enormous. Nearly half of the world's two billion people are afflicted with diseases which can be prevented. More than 300 million persons each year suffer from malaria. In certain underdeveloped areas, one third of the population have syphilis. In some areas, two thirds of the people have trachoma. Yaws, African sleeping sickness and other exotic diseases such as schistosomiasis, filariasis and onchocerciasis are prevalent in some areas to a degree which we in this nation cannot visualize.

Yet, as Dr. Leonard A. Scheele, Surgeon General, Public Health Service, has repeatedly pointed out, there are methods for the control of all of these and many other diseases which prevent people throughout the world from being more economically productive. Malaria-carrying mosquitoes and other insects can be eliminated simply and inexpensively by DDT®. Syphilis, yaws and other infections can be controlled by antibiotics. Aureomycin applied to the eyes of a trachoma victim results in dramatic improvement within a few days. The thread-like worms of filariasis disappear in hours following oral administration of HETRAZAN.® Excellent results are obtained in onchocerciasis with SERAMIN.® The fresh-water snails which transmit schistosomiasis can be killed with chemicals.

Although the United States participated

in the Pan-American Sanitary Bureau and the health activities of the League of Nations for many years, much of our present emphasis on public health outside the U. S. has resulted from our experience in World War II. During and after the war, our military services were faced with enormous practical problems of civilian health in liberated or conquered areas. Our participation in the United Nations Relief and Rehabilitation Administration gave us another opportunity to see the effect of the long continued drain of preventable disease upon human resources.

KEYSTONE of our international health activities is our participation in the World Health Organization, in which some 70 other nations are also active participants. Although active in its formation, the Communist bloc of nations withdrew from W.H.O. two years ago. We in the U. S. have not only supported W.H.O. strongly by paying about one third of its regular budget, but have also supplied it with highly qualified personnel.

Although a relatively young organization, W.H.O. has already had marked success, particularly in its impact programs such as malaria control. Malaria has stifled economic and social progress in the tropics more than any other disease. Now, however, with the perfection of the methods of residual spraying of dwellings, more than 50 million persons throughout the tropical and semitropical regions of the world are protected against malaria by DDT at an annual cost of 20 cents or less per capita.

The economic as well as the social results of these programs have been striking. In one remote corner of Bengal, rice production increased 543 pounds to the acre following a malaria control program. In a formerly malarious district in Greece, the average gross income of local families doubled and the areas cultivated increased by well over half. Within three years in the Philippines, industrial absenteeism dropped from 33 per cent per day to 4 per cent.

Malaria control is but one example. Similar economic returns are being derived from the control of infectious, parasitic and nutritional deficiency diseases, improved sanitation practices, maternal and child welfare programs, and the application of modern public health practices.

Important as these "impact" programs are, leaders in world health recognize that the final aim of W.H.O. is the development of a well-rounded, stable, career national public health service in every country. Such programs will vary, of course, according to the medical, cultural, administrative and financial considerations, but the continuous betterment of public health in each nation will depend upon its own public health service.

Supplementing the work of the W.H.O. and the other international governmental groups such as the United Nations, United Nations International Children's Emergency Fund, United Nations Food and Agriculture Organization, and the United Nations Educational, Scientific and Cultural Organization, our own nation also works bilaterally with a number of underdeveloped nations under the T.C.A., E.C.A. and the Institute of Inter-American Affairs programs. Actual responsibility for program direction and technical guidance in the 10 E.C.A. programs in Greece, Turkey, Formosa, the Philippines, Indonesia, Burma, Thailand, Viet-Nam, Cambodia and Laos and the three T.C.A. projects in Ethiopia, India and Israel rests with the U. S. Public Health Service. The health activities of the Institute of Inter-American Affairs, a separate administrative unit of the Department of State, which serves as the Regional Bureau of the T.C.A. for Latin America is also directed by a Public Health Service officer.

For example, in Burma Public Health Service personnel under E.C.A. are conducting venereal disease control, malaria control, environmental sanitation and nurse training programs. Antibiotics and other drugs are being furnished Indochina and 80,000 persons have been treated with aureomycin in a trachoma control project. Other E.C.A. projects are making substantial contributions to the health of people in Greece,

Formosa, Indonesia, the Philippines, Thailand and Turkey. Similar programs are being sponsored by the T.C.A. in Eritrea, Ethiopia, Iran, Liberia and Jordan. In Latin America, the Institute of Inter-American affairs has given graduate training to 1200 public health workers in the U. S. and 6000 in Latin America and has constructed 85 health centers, 154 water supply systems, 64 sewerage systems and 74 hospitals.

In addition to the work of these governmental groups, many foundations and philanthropic groups such as the Rockefeller Foundation's Division of International Health, the Hadassah Medical Organization, CARE, Unitarian Service Committee, American Bureau for Medical Aid to China, the W. B. Kellogg Foundation, and others are bringing American medical "know how" to various parts of the world. These efforts are also being supplemented by our international professional groups such as the World Medical Association and international specialty bodies and our international voluntary groups such as the International Poliomyelitis Congress, the International Society for the Welfare of Cripples and the League of Red Cross Societies.

There is probably no other aspect of our mutual security in which we in the United States have bought so much with so little. Forty million dollars which we spend on our governmental programs is about the cost of 10 large jet bombers. Communism cannot be contained by military force alone. It thrives in the disease, hunger and poverty which result in human suffering. Our hope in the future lies in improving the health and the social and economic status of the world's underprivileged people.

In these programs to help people help themselves, we are demonstrating to the world our belief in democracy and its better way of life. We are showing that freedom from disease and want can be attained without sacrificing political and social freedom.

HOWARD A. RUSK

PRESCRIBING UNDER BRITAIN'S NATIONAL HEALTH ACT

Estimates indicate that, before the passage of the National Health Act, general practitioners in England usually dispensed drugs for their patients. The report of the Minister of Health says that 80 per cent of practitioners did this and that much of this has disappeared, at least in the towns. On the other hand, only 12 per cent of Scottish doctors used to dispense for their private patients.

Important in consideration of the effects of the National Health Act is the increasing use of proprietary preparations. Under National Health Insurance before the war about 3 per cent of prescriptions were for proprietary preparations. This figure rose to 7 per cent in 1947, to about 12 per cent in the first year of the National Health Service, and to 19 per cent by the end of 1949. This seems to be due to the fact that patients came to their doctors for proprietary prescriptions as a means of getting free supplies and that advice from specialists often included a recommendation for proprietary preparations.

From these facts one may deduce many conclusions as to the effects of the National Health Act on medical practice. Probably the simplest conclusion is that the overwhelming of doctors with patients requiring attention to trivial complaints has resulted in prescribing for proprietaries rather than the more time consuming and difficult composing of a prescription.

MORRIS FISHBEIN

THE GROWTH OF INSURANCE AGAINST THE COSTS OF ILLNESS

The most recent report on accident and health coverage in the United States, prepared by the Survey Committee of the Health Insurance Council, indicates that, at the end of 1950, there were almost 77 million people insured against hospital ex-

pense, almost 55 million against surgical expense and more than 21 million against medical expense. The total increase of 1950 over 1949 was 17 per cent increase for hospital expense, 32 per cent for surgical and 28 per cent for medical.

Protection against medical expenses provided mostly by Blue Shield, the local societies and insurance companies is comparatively recent in its inception but its growth has been rapid. The benefits range from payments toward the expense of doctors' calls in the hospital to comprehensive coverage of home, hospital and office treatments and examinations. The costs of laboratory, x-ray and other examinations for diagnostic purposes may also be included.

The Blue Cross apparently carries about one half of the total insurance against hospital expense—namely, about 39 million persons. Group insurance covers 22 million; individual insurance, 17 million; independent plans about 3.5 million. When deduction is made for estimated duplication, it is necessary to deduct about 5 million people who have duplicate coverage.

The greatest growth in any single type of voluntary health protection has been in the coverage of hospital expense. This no doubt represents the greatest need in the situation. Regions which include heavy concentrations of industry, and therefore of population, also have more hospital expense coverage than do farming and ranching areas but protection is being extended quite rapidly to the rural areas.

MORRIS FISHBEIN

PROBLEMS OF THE BRITISH NATIONAL HEALTH SERVICE

Around February 1 the Conservative Government in Great Britain offered in Parliament a bill proposing changes and charges under the National Health Service. Aneurin Bevan said the proposals meant the "death" of the service. Among other changes is a proposal for fines of one hundred pounds or imprisonment for three months or both for trying to obtain benefits under false pretenses. Once more legislators try to thwart human nature with penalties.

The new bill puts a shilling or 14-cent fee on prescriptions; a maximum fee of one pound or $2.80 on dental treatment; half the cost of wigs, hearing aids, and orthopedic and surgical appliances; charges for the use of day nurseries, and a charge up to 12 shillings daily for private rooms in hospitals. The socialist physicians' organization announced its opposition to the proposals.

Aren't we lucky in the United States that these experiments are being performed on foreign guinea pigs?

MORRIS FISHBEIN

SOCIAL SCIENCE AND HUMAN NATURE

Among the Menominee Indians of Wisconsin, all members of the community are supposed to be on a par. Anyone who becomes outstanding is condemned, criticized and subjected to social opposition. According to James S. Slotkin,[1] assistant professor of social science in the University of Chicago, the Menominee Indian society is a true cooperative where competition between individuals is frowned upon.

What happens when normally aggressive drives are curbed? They break out in other directions. The two main faults are drinking, during which the Indians become boastful and quarrelsome, and gossip which is "universally and deliberately derogatory." Slotkin found that the best people were "moving out of the community" and the incidence of mental and emotional breakdown was unusually high.

Here is a scientific study tending to prove that socialism and communism are against human nature. Slotkin believes that all societies repress some basic or acquired human drives but society pays a price for repression. The highest achievement is voluntary understanding cooperation for the welfare of all.

MORRIS FISHBEIN

1. Research Reports, University of Chicago 2:4 (November) 1951.

THE MEDICAL BOOKMAN

PREVENTIVE MEDICINE AND HYGIENE*

ROSENAU's book has long been recognized as the leading text for students in the field of public health and preventive medicine. The first six editions were edited by the late Dr. Milton J. Rosenau. Since the last edition appeared in 1935, many notable advances have occurred in the field. The present edition was delayed by World War II. Under the direction of its new editor and with the help of 26 contributors of recognized authority, the book has been extensively revised and many portions rewritten. The references at the end of each chapter have also been brought up to date.

The book is divided into nine sections, of which the first is concerned with "Prevention of Communicable Diseases." The discussions in this section are generally complete, conservative and reliable—a pleasant discovery, for there is much in this area that is controversial. Some very recent advances such as the chick-embryo-fluid mumps vaccine are not mentioned but such omissions are few in number. The reviewer feels that passive immunization with antitoxin of adults exposed to diphtheria should have been more strongly condemned. It is an unnecessary procedure and likely to produce a rather high incidence of serious serum sickness.

The discussion on tuberculosis includes the recommendation that the recent trend to build tuberculosis units in urban general hospitals rather than in isolated sanatoriums should be extended. In view of the small risk to medical staffs on a well run chest service and the obvious advantages for the tuberculous patients, it is to be hoped that this trend will be accelerated. It is unfortunate that no mention is made of the very significant contributions made by the United States Army-Navy-Veterans Administration Conferences on the chemotherapy of tuberculosis.

"Nutrition and Deficiency Diseases," the second section, is concise but complete. Section three relates to the "Maintenance of Health and Prevention of Disability." The controversial efforts of governmental agencies to broaden their powers in the field of medicine are presented in a favorable light. A valuable summary of "Food Sanitation" is given in section four, while section five on "Environmental Medicine" includes valuable data on radiation hazards and air pollution.

Following is a discussion of "Industrial Hygiene, Diseases of Occupation," which includes a good summary of such industrial hazards as silicosis and lead and beryllium poisoning. A brief statement concerning the dangers of the use of carbon tetrachloride notes the widespread use of this compound and the frequent lack of information on containers regarding its toxicity. There is no mention of the fact that the concomitant use of alcoholic beverages seems to increase the hazard.

The portion on "Sanitary Control of Water Supplies, Sewage and Refuse Disposal" will be most useful as a reference for persons having responsibilities in this field. There is a good review of breakpoint chlorination of water, a method which should be used more widely in towns and cities. Recent shortages of chlorine supplies, however, are hindering its adoption.

A valuable discussion of epidemiology and a clear presentation of some basic facts concerning medical statistics will be particularly useful for those novices who are bewildered by the usual highly technical treatment of the subject in the standard texts on medical statistics. The book closes with a review of the "Public Health Organization and Activities," which stresses the agencies in the United States.

W. H. H.

(Continued on page A-54)

*Rosenau's Preventive Medicine and Hygiene, by Kenneth F. Maxcy, M.D., Dr.H.P., Johns Hopkins University School of Hygiene and Public Health, Baltimore, Maryland, with the collaboration of 26 contributors. Ed. 7. 1500 pages, 131 illustrations. 1951, Appleton-Century-Crofts, Inc., New York. $14.00.